09/071052

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS 3	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6	Mar 08	Gene Names now available in BIOSIS
NEWS 7	Mar 22	TOXLIT no longer available
NEWS 8	Mar 22	TRCTHERMO no longer available
NEWS 9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
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NEWS 12	Apr 08	"Ask CAS" for self-help around the clock
NEWS 13	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 14	Apr 09	ZDB will be removed from STN
NEWS 15	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 19	Jun 03	New e-mail delivery for search results now available
NEWS 20	Jun 10	MEDLINE Reload
NEWS 21	Jun 10	PCTFULL has been reloaded
NEWS 22	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 23	Jul 19	NTIS to be reloaded July 28, 2002

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'HOME' ENTERED AT 12:55:12 ON 22 JUL 2002

=> file uspatfull
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FILE 'USPATFULL' ENTERED AT 12:55:20 ON 22 JUL 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 18 Jul 2002 (20020718/PD)
FILE LAST UPDATED: 18 Jul 2002 (20020718/ED)
HIGHEST GRANTED PATENT NUMBER: US2002091627
HIGHEST APPLICATION PUBLICATION NUMBER: US2002095707
CA INDEXING IS CURRENT THROUGH 18 Jul 2002 (20020718/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 18 Jul 2002 (20020718/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2002
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2002

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>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s sepsis
L1 3847 SEPSIS

=> s dithiocarbo?
L2 1600 DITHIOCARBO?

=> s l1 and l2
L3 1 L1 AND L2

=> d l3

L3 ANSWER 1 OF 1 USPATFULL
AN 2000:4811 USPATFULL
TI Thiol sulfone metalloprotease inhibitors
IN Freskos, John N., Clayton, MO, United States
Abbas, S. Zaheer, Chesterfield, MO, United States
DeCrescenzo, Gary A., St. Charles, MO, United States

Getman, Daniel P., Chesterfield, MO, United States
Heintz, Robert M., Ballwin, MO, United States
Mischke, Brent V., Defiance, MO, United States
McDonald, Joseph J., Ballwin, MO, United States
PA Monsanto Company, St. Louis, MO, United States (U.S. corporation)
PI US 6013649 20000111
AI US 1997-900028 19970722 (8)
PRAI US 1996-22043P 19960722 (60)
DT Utility
FS Granted
LN.CNT 4735
INCL INCLM: 514/237.800
INCLS: 514/239.200; 514/345.000; 514/369.000; 514/386.000; 514/486.000; 514/543.000; 514/546.000; 514/568.000; 514/570.000; 514/571.000; 514/618.000; 514/630.000; 514/707.000; 514/709.000; 544/158.000; 544/159.000; 544/160.000; 546/290.000; 546/339.000; 548/186.000; 548/316.400; 560/011.000; 560/012.000; 560/254.000; 562/429.000; 568/023.000; 568/029.000; 568/031.000; 568/032.000
NCL NCLM: 514/237.800
NCLS: 514/239.200; 514/345.000; 514/369.000; 514/386.000; 514/486.000; 514/543.000; 514/546.000; 514/568.000; 514/570.000; 514/571.000; 514/618.000; 514/630.000; 514/707.000; 514/709.000; 544/158.000; 544/159.000; 544/160.000; 546/290.000; 546/339.000; 548/186.000; 548/316.400; 560/011.000; 560/012.000; 560/254.000; 562/429.000; 568/023.000; 568/029.000; 568/031.000; 568/032.000
IC [6]
ICM: A61K031-535
ICS: A01N043-40; A01N043-78; A01N043-50; A01N037-10; A01N037-02; A01N037-18; A01N041-12
EXF 544/158; 544/159; 544/160; 546/290; 546/339; 548/186; 548/316.4; 560/11; 560/12; 560/254; 562/429; 568/23; 568/29; 568/31; 568/32; 514/237.8; 514/239.2; 514/345; 514/369; 514/386; 514/486; 514/543; 514/546; 514/568; 514/570; 514/571; 514/618; 514/630; 514/707; 514/709
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d his

(FILE 'HOME' ENTERED AT 12:55:12 ON 22 JUL 2002)

FILE 'USPATFULL' ENTERED AT 12:55:20 ON 22 JUL 2002
L1 3847 S SEPSIS
L2 1600 S DITHIOCARBO?
L3 1 S L1 AND L2

=> s l1 and dithiocarba?
8257 DITHIOCARBA?
L4 23 L1 AND DITHIOCARBA?

=> d l4 1-23 bib, ab, kwic

L4 ANSWER 1 OF 23 USPATFULL
AN 2002:92666 USPATFULL
TI Pharmaceutical compositions comprising metal complexes
IN Bridger, Gary J., Bellingham, WA, UNITED STATES
Cameron, Beth R., Langley, CANADA
Fricker, Simon P., Langley, CANADA
Abrams, Michael J., Custer, WA, UNITED STATES
Skerlj, Renato, Blaine, WA, UNITED STATES
Baird, Ian, Vancouver, CANADA

PI US 2002049190 A1 20020425
AI US 2000-527450 A1 20000317 (9)
PRAI US 1999-125166P 19990319 (60)
DT Utility
FS APPLICATION
LREP Thomas D Mays Ph D JD, Morrison & Foerster LLP, 2000 Pennsylvania Avenue NW, Suite 5500, Washington, DC, 20006-1888
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 13 Drawing Page(s)
LN.CNT 4309
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of the formula

[M.sub.a(X.sub.bL).sub.cY.sub.dZ.sub.e].sup.nt.+-. Formula I

wherein:

M is a metal ion or a mixture of metal ions;

X is a cation or a mixture of cations;

L is a ligand, or mixture of ligands each containing at least two different donor atoms selected from the elements of Group IV, Group V or Group VI of the Periodic Table;

Y is a ligand or a mixture of the same or different ligands each containing at least one donor atom or more than one donor atom selected from the elements of Group IV, Group V or Group VI of the Periodic Table; and

Z is a halide or pseudohalide ion or a mixture of halide ions and pseudohalide ions; and

wherein: a=1-3; b=0-12; c=0-18; d=0-18; e=0-18; and n=0-10; provided that at least one of c, d and e is 1 or more;

wherein c is 0: b is also 0;

wherein a is 1: c, d and e are not greater than 9; and

wherein a is 2: c, d and e are not greater than 12.

SUMM . . . septic shock, post-ischaemic cerebral damage, migraine and dialysis induced renal hypotension: immunopathologic diseases such as hepatic damage in inflammation and **sepsis** allograft rejection, graft versus host diseases, diabetes and wound healing: neurodegenerative diseases such as cerebral ischaemia, trauma, chronic epilepsy, Alzheimer's. . .

SUMM . . . water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be for example sulphoxide, dialkysulphide, **dithiocarbamate** or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be. . .

DETD . . . water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be for example sulphoxide, dialkysulphide, **dithiocarbamate** or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be. . .

DETD [0562] Synthesis of **dithiocarbamate** ligands

DETD [0572] L-Prolinemethyl ester **dithiocarbamic** acid potassium

salt [KS.sub.2CNProOMe]

DETD . . . either 1,4,7-triazacyclononane (tacn) or 1,4,7-trimethyl-1,4,7-triazacyclononane (Me.sub.3tacn), was suspended in deionized water and heated to 40.degree. C. Two equivalents of the **dithiocarbamic** acid salt was added and the reaction continued for 1-1.5 hours during which time the reaction mixture turned a dark. . .

DETD [0605] Ru(tacn)Cl.sub.3 (0.136 g, 0.40 mmol) was reacted with L-proline methyl ester **dithiocarbamic** acid potassium salt (0.20 g, 0.80 mmol) to yield 0.078 g (25%) product.

DETD . . . [Ru(.mu.-diketonato).sub.2(MeCN).sub.2][CF.sub.3SO.sub.3] (where .beta.-diketonato=acac or dpac) was dissolved in EtOH:H.sub.2O (20:1) to give a blue or green solution. Addition of a **dithiocarbamate** salt resulted in an immediate colour change to red/brown. The mixture was stirred at 70.degree. C. for 4-16 h before the solvent was removed under vacuum and the red/brown residue was purified using column chromatography. The **dithiocarbamate** salts were either purchased from Aldrich (NaS.sub.2CNMe.sub.2.2H.sub.2O) or synthesized according to general procedure F (KS.sub.2CNProK, KS.sub.2CNProOMe, KS.sub.2CNMeIleK).

L4 ANSWER 2 OF 23 USPATFULL

AN 2002:85610 USPATFULL

TI Pharmaceutical combinations for the treatment of stroke and traumatic brain injury

IN Chenard, Bertrand L., Waterford, CT, UNITED STATES
Menniti, Frank S., Mystic, CT, UNITED STATES
Saltarelli, Mario D., Mystic, CT, UNITED STATES

PI US 2002045656 A1 20020418

AI US 2001-947652 A1 20010906 (9)

PRAI US 2000-230944P 20000906 (60)

DT Utility

FS APPLICATION

LREP PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49, NEW YORK, NY, 10017-5612

CLMN Number of Claims: 16

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1777

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to methods of treating traumatic brain injury (TBI) or hypoxic or ischemic stroke, comprising administering to a patient in need of such treatment an NR2B subtype selective N-methyl-D-aspartate (NMDA) receptor antagonist in combination with either: (a) a neutrophil inhibitory factor (NIF); (b) a sodium channel antagonist; (c) a nitric oxide synthase (NOS) inhibitor; (d) a glycine site antagonist; (e) a potassium channel opener; (f) an AMPA/kainate receptor antagonist; (g) a calcium channel antagonist; (h) a GABA-A receptor modulator (e.g., a GABA-A receptor agonist); or (i) an antiinflammatory agent.

SUMM . . . respiratory distress syndrome (ARDS); ischemia-reperfusion injury following myocardial infarction, shock, stroke, and organ transplantation; acute and chronic allograft rejection; vasculitis; **sepsis**; rheumatoid arthritis; and inflammatory skin diseases (Harlan et al., 1990, Immunol. Rev. 114, 5).

SUMM . . . are vitamin E, vitamin A, calcium dobesilate, stobadine, alpha-tocopherol, ascorbic acid, alpha-lipoic acid, corcumin, catalase, prevastatin, N-acetylcysteine, nordihydroguaiaretic acid, pyrrolidine **dithiocarbamate**, LY341122, and Metexyl (4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl).

L4 ANSWER 3 OF 23 USPATFULL
AN 2002:85569 USPATFULL
TI Pharmaceutical compositions comprising metal complexes
IN Abrams, Michael J., Glenmore, PA, UNITED STATES
Fricker, Simon P., Berkshire, UNITED KINGDOM
Murrer, Barry A., Berkshire, UNITED KINGDOM
Vaughan, Owen John, Stockholm, SWEDEN
PI US 2002045611 A1 20020418
US 6417182 B2 20020709
AI US 2001-802523 A1 20010309 (9)
RLI Continuation of Ser. No. US 1998-175028, filed on 19 Oct 1998, GRANTED, Pat. No. US 6284752 Continuation of Ser. No. US 1996-602814, filed on 26 Feb 1996, GRANTED, Pat. No. US 5824673
PRAI WO 1994-GB1817 19940819
GB 1993-17686 19930825
DT Utility
FS APPLICATION
LREP Laurie A. Axford, Morrision & Foerster LLP, Suite 500, 3811 Valley Centre Drive, San Diego, CA, 92130-2332
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 915
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB New pharmaceutical compositions and pharmaceutical compositions comprising metal complexes have activity against diseases caused by or related to overproduction or localized high concentration of nitric oxide in the body.
SUMM . . . septic shock, post-ischaemic cerebral damage, migraine, and dialysis induced renal hypotension; immunopathologic diseases such as hepatic damage in inflammation and **sepsis**, allograft rejection, graft versus host diseases, diabetes and wound healing; neurodegenerative diseases such as cerebral ischaemia, trauma, chronic epilepsy, Alzheimer's. . .
SUMM . . . water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be for example sulphoxide, dialkylsulphide, **dithiocarbarnate** or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be. . .
CLM What is claimed:
. . . levels where NO is implicated in disease, according to claim 11, wherein said S donor group is sulphoxide, dialkylsulphide, dialkylcarbamate, **dithiocarbamate**, or dithiophosphate.

L4 ANSWER 4 OF 23 USPATFULL
AN 2002:78389 USPATFULL
TI Preparation of a pathogen inactivated solution of red blood cells having reduced immunogenicity
IN Stassinopoulos, Adonis, Dublin, CA, UNITED STATES
PI US 2002042043 A1 20020411
AI US 2001-872466 A1 20010531 (9)
PRAI US 2000-208962P 20000531 (60)
DT Utility
FS APPLICATION
LREP CERUS CORPORATION, 2525 Stanwell Drive # 300, Concord, CA, 94520
CLMN Number of Claims: 55
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 2177

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds and methods are provided for the preparation of a red blood cell composition which has significantly reduced antigenicity and in which any possible pathogen contaminants have been substantially inactivated. The red blood cell compositions are of particular use for introduction into an individual in cases where the potential for an immune reaction is high, for example in alloimmunized blood recipients or in trauma situations where the possibility of transfusion of a mismatched unit of blood is higher. The red blood cell compositions of this invention provide a much lower risk of transfusion associated disease transmission as well as a much lower risk of a transfusion associated immune reaction.

SUMM . . . the cold (psychrophilic bacteria, e.g. Yersinia enterocolitica, Pseudomonas fluorescens, and Serratia marcescens) are the most common contaminants associated with bacterial **sepsis** after red blood cell transfusion [Gottlieb, Anaesth. Intens. Care 21:20 (1993)]. In order for bacteria to cause morbidity, a certain. . . bacteria, the recipient's constitution, and the characteristics of the blood product (e.g. high or low plasma level, leukofiltration, etc.). Bacterial **sepsis** is due in part to the release of endotoxins from the bacteria. While the growth of psychrophilic bacteria is slowed. . .

DETD . . . or the immune masking compounds. Examples of nucleophilic groups include, but are not limited to, thiol, thioacid, dithioic acid, thiocarbamate, **dithiocarbamate**, amine, phosphate, and thiophosphate groups. Additionally, the nucleophilic group could be an amino group, polyamino group, or a combination of. . .

L4 ANSWER 5 OF 23 USPATFULL

AN 2001:147960 USPATFULL

TI Pharmaceutical compositions comprising metal complexes

IN Abrams, Michael J, Glenmore, PA, United States
Fricker, Simon P, Berkshire, United Kingdom
Murrer, Barry A, Berkshire, United Kingdom
Vaughan, Owen J, Stockholm, Sweden

PA AnorMED Inc., Langley, Canada (non-U.S. corporation)

PI US 6284752 B1 20010904

AI US 1998-175028 19981019 (9)

RLI Continuation of Ser. No. US 602814, now patented, Pat. No. US 5824673

PRAI DE 1993-17686 19930825

DT Utility

FS GRANTED

EXNAM Primary Examiner: Weddington, Kevin E.

LREP Morrison & Foerster LLP

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 921

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB New pharmaceutical compositions and pharmaceutical compositions comprising metal complexes have activity against diseases caused by or related to overproduction or localised high concentration of nitric oxide in the body.

SUMM . . . septic shock, post-ischaemic cerebral damage, migraine, and dialysis induced renal hypotension; immunopathologic diseases such as hepatic damage in inflammation and **sepsis**, allograft rejection, graft versus host diseases, diabetes and wound healing; neurodegenerative diseases such as cerebral ischaemia, trauma, chronic epilepsy, Alzheimer's. . .

SUMM . . . water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be

for example sulphoxide, dialkylsulphide, **dithiocarbamate** or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be. . .

L4 ANSWER 6 OF 23 USPATFULL
AN 2001:86460 USPATFULL
TI Methods of use for peroxynitrite decomposition catalysts, pharmaceutical compositions therefor
IN Stern, Michael K., 1075 Wilson Ave., University City, MO, United States 63130
Salvemini, Daniela, 1651 Timber Ridge Estates Dr., Ballwin, MO, United States 63011
PI US 6245758 B1 20010612
AI US 1996-709788 19960909 (8)
RLI Continuation of Ser. No. US 1995-431593, filed on 1 May 1995
Continuation-in-part of Ser. No. US 1994-242498, filed on 13 May 1994, now abandoned
DT Utility
FS GRANTED
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: Sripada, Pavanaram K
LREP Monsanto Company
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 1526
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a method for the treatment of diseases by the decomposition of peroxynitrite, preferably decomposition to benign products, comprising the use of a complex which is a selected ligand structure providing a complexed metal such as Mn, Fe, Ni and V transition metals. The method of use, as well as novel pharmaceutical compositions therefor, are for the treatment of diseases advantageously affected by decomposition of peroxynitrite ed at a rate over the natural background rate of decay of peroxynitrite in humans suffering from the disease which comprises administration of an amount of a complex, in dosage unit form, which is effective for such acceleration of the decomposition of peroxynitrite .
SUMM These diseases include ischemic reperfusion injuries such as stroke, head trauma and myocardial ischemia, **sepsis**, chronic or acute inflammation (such as arthritis and inflammatory bowel disease and the like), adult respiratory distress syndrome, cancer, bronchopulmonary. . . porphyrin complexes), multiple sclerosis, parkinson's disease, familial amyotrophic lateral sclerosis, and colitis and specific neuronal disorders, preferably ischemic reperfusion, inflammation, **sepsis**, multiple sclersis, parkinson's disease and stroke.
SUMM . . . aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl **dithiocarbamate** , aryl **dithiocarbamate**, alkyl aryl **dithiocarbamate**, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroanitmonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate,. . .
CLM What is claimed is:
. . . A method of claim 1 wherein the disease is ischemic reperfusion, a side effects from drug treatment of cancer, inflammation, **sepsis** , stroke, multiple sclerosis or parkinson's disease.

4. A method of claim 2 wherein the disease is **sepsis**.

11. A method of claim 1 wherein the metal complex is of the formula ##STR13## wherein R.sub.3, R.sub.6, R.sub.9 or. . . aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate, aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl **dithiocarbamate**, aryl **dithiocarbamate**, alkyl aryl **dithiocarbamate**, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroanitmonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate,. . .

L4 ANSWER 7 OF 23 USPATFULL
AN 2001:79141 USPATFULL
TI Immunostimulatory nucleic acid molecules
IN Krieg, Arthur M., Iowa City, IA, United States
Kline, Joel N., Iowa City, IA, United States
PA University of Iowa Research Foundation, Iowa City, IA, United States (U.S. corporation)
Coley Pharmaceutical Group, Inc., Wellesley, MA, United States (U.S. corporation)
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
PI US 6239116 B1 20010529
AI US 1997-960774 19971030 (8)
RLI Continuation-in-part of Ser. No. US 1996-738652, filed on 30 Oct 1996
DT Utility
FS Granted
EXNAM Primary Examiner: Martinell, James
LREP Wolf, Greenfield & Sacks, P.C.
CLMN Number of Claims: 49
ECL Exemplary Claim: 1
DRWN 19 Drawing Figure(s); 19 Drawing Page(s)
LN.CNT 3249
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Nucleic acid sequences containing unmethylated CpG dinucleotides that modulate an immune response including stimulating a Th1 pattern of immune activation, cytokine production, NK lytic activity, and B cell proliferation are disclosed. The sequences are also useful a synthetic adjuvant.
DETD Further, **sepsis**, which is characterized by high morbidity and mortality due to massive and nonspecific activation of the immune system may be. . . bacteria that reach concentrations sufficient to directly activate many lymphocytes. Further evidence of the role of CpG DNA in the **sepsis** syndrome is described in Cowdery, J., et. al., (1996) The Journal of Immunology 156:4570-4575.
DETD . . . sufficient to induce a local inflammatory response. Together with the likely role of CpG DNA as a mediator of the **sepsis** syndrome and other diseases our studies suggest possible new therapeutic applications for antimalarial drugs that act as inhibitors of endosomal. . .
DETD . . . the CpG mediated induction of gene expression cells were activated with CpG DNA in the presence or absence of pyrrolidine **dithiocarbamate** (PDTC), an inhibitor of I.kappa.B phosphorylation. These inhibitors of NF.kappa.B activation completely blocked the CpG-induced expression of protooncogene and cytokine. . .

L4 ANSWER 8 OF 23 USPATFULL
AN 2001:52041 USPATFULL
TI Substituted pyridino pentaazamacrocyle complexes having superoxide

dismutase activity
IN Riley, Dennis P., Chesterfield, MO, United States
Neumann, William L., Ballwin, MO, United States
Henke, Susan L., Webster Groves, MO, United States
Lennon, Patrick, Webster Groves, MO, United States
Aston, Karl W., Pacific, MO, United States
Salvemini, Daniela, Chesterfield, MO, United States
Sikorski, James A., Des Peres, MO, United States
Fobian, Yvette M., Labadie, MO, United States
Grapperhaus, Margaret Lanahan, Troy, IL, United States
Kusturin, Carrie L., Edwardsville, IL, United States
PA Monsanto Company, St. Louis, MO, United States (U.S. corporation)
PI US 6214817 B1 20010410
AI US 1999-398120 19990916 (9)
RLI Continuation-in-part of Ser. No. US 1998-57831, filed on 9 Apr 1998
PRAI US 1997-50402P 19970620 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: Sripada, Pavanaram K
LREP Senniger, Powers, Leavitt & Roedel
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 2946
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds which are effective as catalysts for dismutating superoxide and, more particularly, the manganese or iron complexes of substituted, unsaturated heterocyclic pentaazacyclopentadecane ligands which catalytically dismutate superoxide.
DETD . . . aryl guanidino, alkyl aryl guanidino, alkyl carbamate, aryl carbamate, alkyl aryl carbamate, alkyl thiocarbamate aryl thiocarbamate, alkyl aryl thiocarbamate, alkyl **dithiocarbamate**, aryl **dithiocarbamate**, alkyl aryl **dithiocarbamate**, bicarbonate, carbonate, perchlorate, chlorate, chlorite, hypochlorite, perbromate, bromate, bromite, hypobromite, tetrahalomanganate, tetrafluoroborate, hexafluorophosphate, hexafluoroantimonate, hypophosphite, iodate, periodate, metaborate, tetraaryl borate,. . .
DETD . . . refractory hypotension, organ preservation, radiation-induced injury, platelet aggregation, stroke, autoimmune diseases, adult respiratory distress, carcinogenesis, severe chronic pain, hyperalgesia, and **sepsis**. The complexes of this invention are excellent analgesics and can be used to treat or prevent pain in a subject. . .
CLM What is claimed is:
. . . platelet aggregation, stroke, autoimmune diseases, refractory hypotension, adult respiratory distress, carcinogenesis, severe chronic pain, reversal of opioid tolerance, hyperalgesia, and **sepsis**.

. . . of claim 28 wherein said disease or disorder is selected from the group consisting of ischemic reperfusion injury, inflammation, hyperalgesia, **sepsis**, refractory hypotension, stroke, reversal of opioid tolerance, and hypertension.

L4 ANSWER 9 OF 23 USPATFULL
AN 2000:174074 USPATFULL
TI Pharmaceutical compositions containing alkylaryl polyether alcohol polymer
IN Kennedy, Thomas P., Richmond, VA, United States

PA Charlotte-Mecklenburg Hospital Authority, Charlotte, NC, United States (U.S. corporation)
PI US 6165445 20001226
AI US 1998-210032 19981211 (9)
RLI Division of Ser. No. US 1996-638893, filed on 25 Apr 1996, now patented, Pat. No. US 5849263 which is a continuation-in-part of Ser. No. US 1994-299316, filed on 31 Aug 1994, now patented, Pat. No. US 5512270 which is a continuation-in-part of Ser. No. US 1993-39732, filed on 30 Mar 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Harrison, Robert H.
LREP Alston & Bird LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1372
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is provided novel pharmaceutical compositions containing tyloxapol as the active ingredient. These formulations comprise tyloxapol at concentrations above 0.125%, preferably from about 0.25% to about 5.0%. In addition, the invention encompasses pharmaceutical compositions having reduced hypertonicity which compositions comprise tyloxapol in pharmaceutically acceptable solutions without significant concentrations of hypertonic agents or other active ingredients NaHCO.sub.3, or active phospholipids, such as DPPC. The less hypertonic formulations allow one to derive all the benefits of the active ingredient tyloxapol, such as its reduced toxicity and enhanced half-life, while avoiding or reducing side effects, such as bronchospasms, associated with the various hypertonic agents or other active ingredient agents.
SUMM . . . .alpha., IL-1.beta. and IL-6 by human peripheral blood mononuclear cells". International Journal of Immunology (1993) 6:409-422; R. Schreck, et al. "**Dithiocarbamates** as potent inhibitors of nuclear factor .kappa.B activation in intact cells". Journal of Experimental Medicine (1992) 175:1181-1194). However, the few. . .
SUMM . . . oxygen desaturation (EXOSURF Neonatal. 1995. Physicians Desk Reference. Medical Economics, Montvale, N.J. 758-762). EXOSURF has also undergone a trial for **sepsis**-induced adult respiratory distress syndrome in adults (Weg, J. G., R. A. Balk, et al. 1994. Safety and potential efficacy of an aerosollized surfactnat in human **sepsis**-induced adult respiratory distress syndrome. J.A.M.A. 727:1433-1438). Subjects received EXOSURF aerosolized continuously over 12 or 24 hours, respectively for up to. . .

L4 ANSWER 10 OF 23 USPATFULL
AN 2000:37824 USPATFULL
TI Agent for treatment of viral infections
IN Maeda, Hiroshi, 21-19, Hotakubo 3-chome, Kumamoto-shi, Kumamoto 862, Japan
Akaike, Takaaki, Kumamoto, Japan
PA Maeda, Hiroshi, Kumamoto-ken, Japan (non-U.S. individual)
PI US 6043268 20000328
AI US 1996-772852 19961224 (8)
RLI Continuation-in-part of Ser. No. WO 1995-JP65, filed on 23 Jan 1995
PRAI JP 1994-171946 19940629
DT Utility
FS Granted
EXNAM Primary Examiner: Travers, Russell
LREP Birch, Stewart, Kolasch & Birch, LLP

CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 610
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treatment of viral infections which comprises administering to the patients being suffering from said viral infections an effective amount of one or more substances selected from the group consisting of nitric oxide scavengers and nitric oxide synthase inhibitors. Said method for treatment of viral infections is useful in viral infections induced by influenza virus, herpes virus, hepatitis virus, cytomegalovirus, human immunodeficiency virus, etc.
SUMM . . . indicated that overproduced .cndot.NO damages various tissues based on the chemical reactivity of .cndot.NO as a radical in cases of **sepsis**, endotoxin shock, arthritis, etc., as explained above. Under the above circumstances, the present inventors have intensively studied and paid much. . .
DETD (iii) N-Methyl-D-glucamine **dithiocarbamate** (MGD)
CLM What is claimed is:
. . . wherein R is a hydrogen atom, a carboxyl group, a carboxymethoxy group, or a pharmaceutically acceptable salt thereof, 3-(3,4-dihydroxy-5-nitrobenzylidene)-2,4-pentadione, N-methyl-D-glucamine **dithiocarbamate**, L-arginine analogues selected from N.sup.G -nitro-L-arginine, N.sup.G -amino-L-arginine, N.sup.G -monomethyl-L-arginine, N.sup.G, N.sup.G -dimethyl-L-arginine, N.sup.G -nitro-L-arginine methyl ester, or a pharmaceutically. . .

L4 ANSWER 11 OF 23 USPATFULL
AN 2000:12778 USPATFULL
TI Preparation having increased in vivo tolerability
IN Bosslet, Klaus, Gaithersburg, MD, United States
Czech, Jorg, Marburg, Germany, Federal Republic of
Gerken, Manfred, Marburg, Germany, Federal Republic of
Straub, Rainer, Marburg, Germany, Federal Republic of
Blumrich, Matthias, Wettenberg, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 6020315 20000201
AI US 1998-76878 19980513 (9)
PRAI DE 1997-19720312 19970515
DT Utility
FS Granted
EXNAM Primary Examiner: Lee, Howard C.
LREP Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 528
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A preparation having increased in vivo tolerability comprising a glycosyl-Y[--C(.dbd.Y)--X--].sub.p --W(R).sub.n --X--C(.dbd.Y)-active compound, sugar or sugar alcohol and, optionally divalent ions, and a pharmaceutically tolerable carrier.
SUMM . . . mifepristone, onapristone, N-(4-aminobutyl)-5-chloro-2-naphthalenesulfonamide, pyridinyloxazol-2-one, quinolyl- or isoquinolyloxazol-2-one, staurosporin, ethanolamine, verapamil, forskolin, 1,9-dideoxyforskolin, quinine, quinidine, reserpine, 18-O-(3,5-dimethoxy-4-hydroxybenzoyl)-reserpate, lonidamine, buthionine sulfoximine, diethyl **dithiocarbamate**, cyclosporin A, rapamycin, azathioprine, chlorambucil, hydroxycrotonamide derivative 2,

leflunomide, 15-deoxyspergualine, FK 506, ibuprofen, indomethacin, aspirin, sulfasalazine, penicillamine, chloroquine, dexamethasone, prednisolone,. . .
SUMM acute immunological events such as **sepsis**, allergy, graft-versus-host and host-versus-graft reactions

L4 ANSWER 12 OF 23 USPATFULL
AN 1999:78766 USPATFULL
TI Methods for in vivo reduction of iron levels and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5922761 19990713
AI US 1996-708552 19960906 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Gray Cary Ware & Freidenrich LLP, Reiter, Stephen E.
CLMN Number of Claims: 40
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1065
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB In accordance with the present invention, there are provided methods for the in vivo reduction of free iron ion levels in a mammalian subject. The present invention employs a scavenging approach whereby free iron ions are bound in vivo to a suitable physiologically compatible scavenger. The resulting complex renders the free iron ions harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-containing composition. This material binds to free iron ions, forming a stable, water-soluble **dithiocarbamate**-iron complex. The present invention relates to methods for reducing in vivo levels of free iron ions as a means of treating subjects afflicted with iron overload and non-iron overload diseases and/or conditions, such as thalassemia, anemia hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. **Dithiocarbamate**-containing scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo forming a stable **dithiocarbamate**-metal complex, which is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo levels of free iron ions.
AB . . . carrying out the above-described methods. An exemplary scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-containing composition. This material binds to free iron ions, forming a stable, water-soluble **dithiocarbamate**-iron complex. The present invention relates to methods for reducing in vivo levels of free iron ions as a means of. . . with iron overload and non-iron overload diseases and/or conditions, such as thalassemia, anemia hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. **Dithiocarbamate**-containing scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo forming a stable **dithiocarbamate**-metal complex, which is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing. . .
SUMM . . . a particular aspect, the present invention relates to methods

for reducing free iron ion levels in mammals by administration of **dithiocarbamates** as scavengers of free iron ions in hosts undergoing anthracycline chemotherapy, as well as hosts suffering from iron overload or. . .

SUMM An exemplary physiologically compatible scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-based formulation. **Dithiocarbamates** according to the invention bind to free iron ions, forming a stable, water-soluble **dithiocarbamate**-iron complex. **Dithiocarbamates** are a class of low molecular-weight sulphur-containing compounds that are effective chelators (see, for example, Shinobu et al., in Acta. . .

SUMM **Dithiocarbamates**, such as N-methyl-D-glucamine **dithiocarbamate** (MGD), chelate with ferrous or ferric iron to form a stable and water-soluble two-to-one [(MGD).sub.2 -Fe.sup.2+] or [(MGD).sub.2 -Fe.sup.3+. . .

SUMM . . . the release of cellular iron from tissues (see, for example, Kim et al., in J. Biol. Chem. 270:5710-5713 (1995)). Thus, **dithiocarbamates** such as MGD are capable of removing free iron in vivo, particularly during the infectious and inflammatory conditions where intracellular. . .

DRWD FIG. 1 provides UV-visible spectra of N-methyl-D-glucamine **dithiocarbamate** (MGD) and [MGD-Fe] complexes in aqueous solution.

DETD Exemplary physiologically compatible compounds contemplated for use in the practice of the present invention are **dithiocarbamates**. These materials are said to be "physiologically compatible" because they do not induce any significant side effects. In other words,. . .

DETD **Dithiocarbamate** compounds contemplated for use in the practice of the present invention include any physiologically compatible derivative of the **dithiocarbamate** moiety (i.e., (R).sub.2 N--C(S)--SH). Such compounds can be described with reference to the following generic structure:

DETD In accordance with a particular aspect of the present invention, the **dithiocarbamate**-containing iron scavenger is administered in combination with a cytokine (e.g., IL-1, IL-2, IL-6, IL-11, IL-12, TNF or interferon-.gamma.) , an. . . of the above-noted pharmaceutical agents (e.g., induction of release of free iron ions) can be prevented or reduced by the **dithiocarbamate**-containing scavenger. Thus, a patient being treated with any of the above-described agents could be monitored for evidence of elevated free. . . At the first evidence of such elevated levels of free iron ions, co-administration of a suitable dose of the above-described **dithiocarbamate**-containing scavenger could be initiated, thereby alleviating (or dramatically reducing) the side-effects of the primary therapy.

DETD Those of skill in the art recognize that the **dithiocarbamate**-containing scavengers described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally,. . .

DETD . . . administration and dosage employed for each subject is left to the discretion of the practitioner. In general, the dosage of **dithiocarbamate**-containing scavengers employed in the practice of the present invention falls in the range of about 5 mg-18.5 g/day. Presently preferred. . .

DETD . . . delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like. Depending on the mode of delivery employed, the **dithiocarbamate**-containing scavenger can be delivered in a variety of pharmaceutically acceptable forms. For example, the scavenger can be delivered in the. . .

DETD . . . accordance with yet another embodiment of the present invention, there are provided compositions comprising an anthracycline

anti-cancer agent and a **dithiocarbamate** having the structure I, as described above.

DETD UV-visible Spectra of N-methyl-D-glucamine **dithiocarbamate** and MGD-Fe Complex

DETD N-methyl-D-glucamine **dithiocarbamate** synthesized by Shinobu et al's method (Shinobu et al., supra) was highly pure as determined by element analysis and by. . .

DETD . . . released by excessive NO production, which is known to attack cellular iron-containing proteins and result in cellular iron loss during **sepsis** or septic shock (see, for example, Kim et al., in J. Biol. Chem. 270:5710-5713 (1995)). In other words, upon intravenous. . .

CLM What is claimed is:

. . . are elevated above normal, said method comprising: administering to said subject an effective amount of at least one physiologically compatible **dithiocarbamate** capable of binding free iron ions, wherein said **dithiocarbamate** has the formula: [R.sub.1 R.sub.2 N--C(S)--S.sup.-]M.sup.+1 (I) wherein: each of R.sub.1 and R.sub.2 is independently selected from a C.sub.1. . .

. . . of free iron ions, said method comprising: administering to said subject an effective amount of at least one physiologically compatible **dithiocarbamate** capable of binding free iron ions, wherein said **dithiocarbamate** has the formula: [R.sub.1 R.sub.2 N--C(S)--S.sup.-]M.sup.+1 (I) wherein: each of R.sub.1 and R.sub.2 is independently selected from a C.sub.1. . .

. . . ions in a subject, said method comprising: administering to said subject an effective amount of at least one physiologically compatible **dithiocarbamate** capable of binding free iron ions, wherein said **dithiocarbamate** has the formula: [R.sub.1 R.sub.2 N--C(S)--S.sup.-]M.sup.+1 (I) wherein: each of R.sub.1 and R.sub.2 is independently selected from a C.sub.1. . .

23. A method according to claim 14 wherein said **dithiocarbamate** is administered in combination with a cytokine, an antibiotic, a vasoactive agent, or mixtures thereof.

26. A method according to claim 14 wherein said **dithiocarbamate** is delivered orally, intravenously, subcutaneously, parenterally, rectally or by inhalation.

27. A method according to claim 14 wherein said **dithiocarbamate** is delivered in the form of a solid, solution, emulsion, dispersion, micelle or liposome.

35. A method according to claim 15 wherein said **dithiocarbamate** is administered in combination with a cytokine, an antibiotic, a vasoactive agent, or mixtures thereof.

38. A method according to claim 15 wherein said **dithiocarbarnate** is delivered orally, intravenously, subcutaneously, parenterally, rectally or by inhalation.

39. A method according to claim 15 wherein said **dithiocarbamate** is delivered in the form of a solid, solution, emulsion, dispersion, micelle or liposome.

40. A composition comprising adriamycin or liposomal adriamycin, plus **dithiocarbamate**.

AN 1998:156887 USPATFULL
TI Pharmaceutical compositions containing alkylaryl polyether alcohol polymer
IN Kennedy, Thomas P., Richmond, VA, United States
PA Charlotte-Mecklenburg Hospital Authority, Charlotte, NC, United States (U.S. corporation)
PI US 5849263 19981215
AI US 1996-638893 19960425 (8)
RLI Continuation-in-part of Ser. No. US 1994-299316, filed on 31 Aug 1994, now patented, Pat. No. US 5512270 which is a continuation-in-part of Ser. No. US 1993-39732, filed on 30 Mar 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Harrison, Robert H.
LREP Bell Seltzer Intellectual Property Law Group of Alston & Bird LLP
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1385
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is provided novel pharmaceutical compositions containing tyloxapol as the active ingredient. These formulations comprise tyloxapol at concentrations above 0.125%, preferably from about 0.25% to about 5.0%. In addition, the invention encompasses pharmaceutical compositions having reduced hypertonicity which compositions comprise tyloxapol in pharmaceutically acceptable solutions without significant concentrations of hypertonic agents or other active ingredients NaHCO.sub.3, or active phospholipids, such as DPPC. The less hypertonic formulations allow one to derive all the benefits of the active ingredient tyloxapol, such as its reduced toxicity and enhanced half-life, while avoiding or reducing side effects, such as bronchospasms, associated with the various hypertonic agents or other active ingredient agents.
SUMM . . . .beta., IL-1.beta. and IL-6 by human peripheral blood mononuclear cells". International Journal of Immunology (1993) 6:409-422; R. Schreck, et al. "**Dithiocarbamates** as potent inhibitors of nuclear factor .kappa.B activation in intact cells". Journal of Experimental Medicine (1992) 175:1181-1194). However, the few. . .
SUMM . . . oxygen desaturation (EXOSURF Neonatal. 1995. Physicians Desk Reference. Medical Economics, Montvale, N.J. 758-762). EXOSURF has also undergone a trial for **sepsis**-induced adult respiratory distress syndrome in adults (Weg, J. G., R. A. Balk, et al. 1994. Safety and potential efficacy of an aerosollized surfactnat in human **sepsis**-induced adult respiratory distress syndrome. J.A.M.A. 727:1433-1438). Subjects received EXOSURF aerosolized continuously over 12 or 24 hours, respectively for up to. . .

L4 ANSWER 14 OF 23 USPATFULL
AN 1998:154309 USPATFULL
TI Method for in vivo reduction of nitric oxide levels and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, United States
PA MCW Research Foundation, Milwaukee, WI, United States (U.S. corporation)
PI US 5847004 19981208
AI US 1996-767125 19961209 (8)
RLI Continuation-in-part of Ser. No. US 1995-554196, filed on 6 Nov 1995 which is a continuation-in-part of Ser. No. US 1995-459518, filed on 2 Jun 1995, now patented, Pat. No. US 5741815
DT Utility
FS Granted

EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Smith, Lyman H.
LREP Gray Cary Ware and Freidenrich, Reiter, Stephen E.
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1485
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In accordance with the present invention, there are provided methods for the in vivo reduction of nitric oxide levels in a mammalian subject. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for nitric oxide production is inhibited), the present invention employs a scavenging approach whereby overproduced nitric oxide is bound in vivo to a suitable nitric oxide scavenger. The resulting complex renders the nitric oxide harmless, and is eventually excreted in the urine of the host. An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble NO-containing complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy. The present invention relates to methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. Nitric oxide scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable NO-containing complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo .NO levels.

AB . . . of the host. An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble NO-containing complex having a characteristic three-line spectrum (indicative of. . .

SUMM An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds non-covalently to .NO, forming a stable, water-soluble **dithiocarbamate**-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by. . .

DRWD . . . 1C illustrate the effects of .NO inhibitors on ex-vivo 9.5-GHz EPR spectra of the [(MGD).sub.2 /Fe--NO] complex (MGD is N-methyl-D-glucamine **dithiocarbamate**) detected in the urine of normal mice. The mice were injected subcutaneously with 0.4 mL of the [(MGD).sub.2 /Fe] complex. . .

DETD Physiologically compatible compounds contemplated for use in the practice of the present invention include any physiologically compatible derivative of the **dithiocarbamate** moiety (i.e., (R).sub.2 N--C(S)--SH), chalating agents, and the like.

DETD Suitable **dithiocarbamate** compounds contemplated for use in the practice of the present invention can be described with reference to the following generic. . .

DETD Presently preferred **dithiocarbamate** compounds having the above-described generic structure are those wherein:

DETD Especially preferred **dithiocarbamate** compounds having the above-described generic structure are those wherein:

DETD The presently most preferred **dithiocarbamate** compounds having the above-described generic structure are those wherein:

DETD Monovalent cations contemplated for incorporation into the above-described **dithiocarbamate** compounds include H.sup.+,

Na.sup.+, NH.sub.4.sup.+, tetraalkyl ammonium, and the like. Physiologically compatible divalent or trivalent transition metal cations contemplated for incorporation into the above-described **dithiocarbamate** compounds include charged forms of iron, cobalt, copper, manganese, or the like (e.g., Fe.sup.+2, Fe.sup.+3, Co.sup.+3, Cu.sup.+2 , Mn.sup.+2 or Mn.sup.+3). In accordance with the present invention, the ratio of **dithiocarbamate**-species to counter-ion M can vary widely. Thus, **dithiocarbamate**-containing nitric oxide scavenger can be administered without any added metallic counter-ion (i.e., M=H.sup.+, or a transition metal cation to **dithiocarbamate**-species ratio of zero), with ratios of transition metal cation to **dithiocarbamate**-species up to about 1:2 (i.e., a 2:1 **dithiocarbamate**:transition metal cation complex) being suitable.

DETD . . . delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like. As noted above, compounds of structure I (i.e., **dithiocarbamate**-species free of transition metal cations) can be employed directly in the practice of the present invention, or pre-formed **dithiocarbamate**-transition metal chelates (i.e., compounds of structure II) having varying ratios of transition metal to **dithiocarbamate**-species can be employed in the invention methods.

DETD Also contemplated are compositions representing a combination of compounds of structure I and compounds of structure II, i.e., **dithiocarbamate** species wherein the ratio of M.sup.+1 : **dithiocarbamate**-species is less than 1:1 and the ratio of M.sup.+2,+3 :**dithiocarbamate**-species is less than 1:2. A presently preferred composition is one wherein the ratio of M.sup.+2,+3 :**dithiocarbamate**-species is about 1:5 (i.e., about 40% of the **dithiocarbamate**-species are incorporated into a **dithiocarbamate**:transition metal cation complex, while about 60% of the **dithiocarbamate**-species exist in monovalent form).

DETD N-Methyl-D-glucamine and carbon disulfide were obtained from Aldrich (Milwaukee, Wis.). N-Methyl-D-glucamine **dithiocarbamate** (MGD) was synthesized by following the method of Shinobu et al. (Acta Pharmacol. Toxicol. 54:189-194 (1984)).

DETD . . . released by excess .NO production, which is known to attack cellular iron-containing proteins and result in cellular iron loss during **sepsis** or septic shock. This example shows that MGD, either with or without added iron, is effective for the treatment of. . .

L4 ANSWER 15 OF 23 USPATFULL
AN 1998:128261 USPATFULL
TI Pharmaceutical compositions comprising metal complexes
IN Abrams, Michael J., Glenmore, PA, United States
Fricker, Simon P., Berkshire, United Kingdom
Murrer, Barry A., Berkshire, United Kingdom
Vaughan, Owen J., Stockholm, Sweden
PA Johnson Matthey Public Limted Company, London, England (non-U.S. corporation)
PI US 5824673 19981020
WO 9505814 19950302
AI US 1996-602814 19960226 (8)
WO 1994-GB1817 19940819
19960226 PCT 371 date
19960226 PCT 102(e) date
PRAI GB 1993-17686 19930825
DT Utility
FS Granted

EXNAM Primary Examiner: Weddington, Kevin E.
LREP Pillsbury Madison & Sutro LLP
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 847
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB New pharmaceutical compositions and pharmaceutical compositions comprising metal complexes have activity against diseases caused by or related to overproduction or localized high concentration of nitric oxide in the body.
SUMM . . . septic shock, post-ischaemic cerebral damage, migraine, and dialysis induced renal hypotension; immunopathologic diseases such as hepatic damage in inflammation and **sepsis**, allograft rejection, graft versus host diseases, diabetes and wound healing; neurodegenerative diseases such as cerebral ischaemia, trauma, chronic epilepsy, Alzheimer's. . .
SUMM . . . water, oxide, sulphoxide, hydroxide, acetate, lactate, propionate, oxalate and maltolate. Suitable sulphur donor groups may be for example sulphoxide, dialkylsulphide, **dithiocarbamate** or dithiophosphate. Suitable carbon donor groups may be for example carbon monoxide or isocyanide. Suitable phosphorus donor groups may be. . .
CLM What is claimed is:
10. The method of claim 1 wherein the donor atom is sulphur present as dialkylsulphide, dialkylcarbamate, **dithiocarbamate**, or dithiophosphate.

L4 ANSWER 16 OF 23 USPATFULL
AN 1998:61456 USPATFULL
TI Osteoarthritis-associated inducable isoform of nitric oxide synthetase
IN Amin, Ashok R., Union, NJ, United States
Abramson, Steven B., Rye, NY, United States
PA Hospital For Joint Diseases, New York, NY, United States (U.S. corporation)
PI US 5759836 19980602
AI US 1995-410739 19950327 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Weber, Jon P.
LREP Browdy and Neimark
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 2100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An novel isoform of inducible nitric oxide synthase (OA-NOS) has been identified in osteoarthritis-affected articular cartilage. Some properties, including molecular weight, are similar to the constitutive isoform of neuronal nitric oxide synthase (ncnos) while other properties share similarity with the previously identified inducible nitric oxide (iNOS). Acetylating agents, such as aspirin and N-acetylimidazole act on both iNOS and OA-NOS by inhibiting their catalytic activities. A method is provided to screen for acetylating agents that inhibit OA-NOS, and the selective inhibition of OA-NOS by inhibitory agents is determined by comparison to a panel of different isoforms of nitric oxide synthase.
SUMM . . . synthesis becomes self-destructive, as is known in disorders such as autoimmune disease, immune rejection of allografted organs, graft-versus-host disease, and **sepsis**. However, these pro-inflammatory effects of NO are not evident under acute physiological

conditions, in which it can mediate anti-inflammatory functions. . .
DETD . . . the integral components of iNOS transcription/expression (Xie et al., 1994, supra), which can be inhibited by an NF-.kappa.B inhibitor, pyrrolidine **dithiocarbamate** at 30 .mu.M. Our studies indicate that 3 mM aspirin is probably not sufficient to block the transcription of the iNOS gene, as observed with 30 .mu.M of pyrrolidine **dithiocarbamate**, which blocked >90% of nitrite accumulation in our studies (data not shown). Furthermore, the lack of significant effect of aspirin. . .
DETD . . . were obtained from Affinity Bioreagents, Inc. (Neshanic Station, N.J.) anti-calmodulin antibodies from UBI (Lake Placid, N.Y.), protease inhibitors, cycloheximide, pyrrolidine **dithiocarbamate** (PDTC), aminoguanidine and LPS from Sigma (St. Louis, Mo.), human IL-1.beta. and TNF-.alpha. from Fisher Scientific (Springfield, N.J.), and L-NMMA. . .
CLM What is claimed is:
. . . antibody; (C) lack of reactivity to .alpha.-iNOS polyclonal antibody; (D) binding calmodulin; (E) inhibited by cycloheximide; (F) inhibited by pyrrolidone **dithiocarbamate**; (G) inhibited by 200 .mu.M aminoguanidine and N.sup.G -monomethyl-L-arginine monoacetate; (H) inhibited by 1-3 mM aspirin; (I) inhibited by 5-10. . .

L4 ANSWER 17 OF 23 USPATFULL
AN 1998:48450 USPATFULL
TI Combinational therapeutic methods employing nitric oxide scavengers and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5747532 19980505
AI US 1995-561594 19951121 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Smith, Lyman H.
LREP Gray Cary Ware & Freidenrich, Reiter, Stephen E.
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1112
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB In accordance with the present invention, there are provided combinational therapeutic methods for the in vivo inactivation or inhibition of formation (either directly or indirectly) of species which induce the expression of nitric oxide synthase, as well as reducing nitric oxide levels produced as a result of .NO synthase expression. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for nitric oxide production is inhibited), the present invention employs a combination of inactivation (or inhibition) and scavenging approach whereby the stimulus of nitric oxide synthase expression is inactivated, or the production thereof is inhibited, and overproduced nitric oxide is bound in vivo to a suitable nitric oxide scavenger. The resulting complexes render the stimulus of nitric oxide synthase expression inactive (or inhibit the production thereof), and nitric oxide harmless. The resulting complexes are eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods.
SUMM . . . reducing nitric oxide levels, by co-administration of agents which inactivate (or inhibit the production of) such species, along with a **dithiocarbamate** compound as a scavenger of overproduced

nitric oxide. In a further aspect, the present invention relates to compositions and formulations. . .

SUMM An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble **dithiocarbamate**-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by. . .

SUMM . . . of inactivating species which induce expression of inducible nitric oxide, or agents which inhibit the production of such species, and **dithiocarbamate**-containing nitric oxide scavengers) are administered to a host in need of such treatment. The agent capable of inactivating (or inhibiting. . . and in vivo produced .NO, respectively, forming a complex between said species and said agent, as well as a stable **dithiocarbamate**-metal-NO complex. Whereas free -NO is a potent vasodilator, .NO chelated with **dithiocarbamate**-iron complexes is not. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by. . .

DETD . . . one agent capable of directly or indirectly inactivating said species, or inhibiting production of said species, and at least one **dithiocarbamate**-containing nitric oxide scavenger.

DETD **Dithiocarbamate**-containing nitric oxide scavengers contemplated for use in the practice of the present invention include any physiologically compatible derivative of the **dithiocarbamate** moiety (i.e., (R).sub.2 N--C(S)--SH). Such compounds can be described with reference to the following generic structure (I)

DETD . . . the like (e.g., Fe.sup.+2, Fe.sup.+3, Co.sup.+2, Co.sup.+3, Cu.sup.+2, Mn.sup.+2 or Mn.sup.+3). In accordance with the present invention, the ratio of **dithiocarbamate**-species to counter-ion M can vary widely. Thus, **dithiocarbamate**-containing nitric oxide scavenger can be administered without any added metallic counter-ion (i.e., M=H.sup.+, or a transition metal cation to **dithiocarbamate**-species ratio of zero), with ratios of transition metal cation to **dithiocarbamate**-species up to about 1:2 (i.e., a 2:1 **dithiocarbamate**:transition metal cation complex) being suitable.

DETD In accordance with a particular aspect of the present invention, the **dithiocarbamate**-containing nitric oxide scavenger is administered in combination with one or more of the above-described agents, optionally including an antibiotic (e.g.,. . . are designed to address (e.g., systemic hypotension) can be prevented or reduced by co-administration of a combination reagent including a **dithiocarbamate**-containing nitric oxide scavenger.

DETD . . . which induce the expression of inducible nitric oxide (or an agent capable of inhibiting the production of such species), and **dithiocarbamate**-containing nitric oxide scavengers described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously,. . .

DETD Typical daily doses of **dithiocarbamate**-containing nitric oxide scanvengers, in general, lie within the range of from about 10 .mu.g up to about 100 mg per. . .

DETD In general, the dosage of **dithiocarbamate**-containing nitric oxide scavenger employed in the practice of the present invention falls in the range of about 0.01 mmoles/kg body. . .

DETD N-Methyl-D-glucamine and carbon disulfide were obtained from Aldrich (Milwaukee, Wis.). N-Methyl-D-glucamine **dithiocarbamate** (MGD) was synthesized by following the method of Shinobu et al. (Acta Pharmacol. Toxicol. 54:189-194 (1984)).

DETD . . . released by excess .NO production, which is known to attack

cellular iron-containing proteins and result in cellular iron loss during **sepsis** or septic shock (see, for example, Kim et al., in J. Biol. Chem. 270:5710-5713 (1995)).

DETD This example shows that **dithiocarbamate**-containing nitric oxide scavengers, such as MGD, either with or without added iron, are effective for the treatment of systemic hypotension,. . .

CLM What is claimed is:

. . . one agent capable of directly or indirectly inactivating said species, or inhibiting production of said species, and at least one **dithiocarbamate**-containing nitric oxide scavenger.

5. A method according to claim 1 wherein said **dithiocarbamate** -containing nitric oxide scavenger comprises a **dithiocarbamate** moiety having the structure (I), optionally associated with a physiologically compatible di- or tri-valent transition metal ion, wherein structure (I). . .

6. A method according to claim 5 wherein the ratio of transition metal ion to **dithiocarbamate** moiety falls in the range of zero up to about 1:2.

8. A method according to claim 1 wherein said combination of at least one agent, and at least one **dithiocarbamate**-containing nitric oxide scavenger is delivered orally, intravenously, subcutaneously, parenterally, rectally or by inhalation.

9. A method according to claim 1 wherein said combination of at least one agent, and at least one **dithiocarbamate**-containing nitric oxide scavenger is delivered in the form of a solid, solution, emulsion, dispersion, micelle or liposome.

. . . indirectly, induce the expression of inducible nitric oxide synthase, the improvement comprising co-administering to a patient in need thereof a **dithiocarbamate**-containing nitric oxide scavenger in combination with said agent.

15. A composition according to claim 12 wherein the ratio of transition metal ion to **dithiocarbamate** moiety falls in the range of zero up to about 1:2.

L4 ANSWER 18 OF 23 USPATFULL
AN 1998:42383 USPATFULL
TI Methods for in vivo reduction of nitric oxide levels and compositions useful therefor
IN Lai, Ching-San, 17765 Bolter La., Brookfield, WI, United States 53045
PI US 5741815 19980421
AI US 1995-554196 19951106 (8)
RLI Continuation-in-part of Ser. No. US 1995-459518, filed on 2 Jun 1995
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Smith, Lyman H.
LREP Gray Cary Ware & Freidenrich, Reiter, Stephen E.
CLMN Number of Claims: 41
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1537
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention employs a scavenging approach whereby overproduced nitric oxide is bound in vivo to a suitable nitric oxide scavenger. The resulting complex renders the nitric oxide harmless, and is eventually

excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble **dithiocarbamate**-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy. The present invention relates to methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. **Dithiocarbamate**-containing nitric oxide scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable **dithiocarbamate**-metal-NO complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo .NO levels.

AB . . . the above-described methods. An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble **dithiocarbamate**-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by. . . methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. **Dithiocarbamate**-containing nitric oxide scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable **dithiocarbamate**-metal-NO complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject,. . .

SUMM . . . In a particular aspect, the present invention relates to methods for reducing nitric oxide levels in mammals by administration of **dithiocarbamate**-metal complexes as scavengers of nitric oxide in hosts afflicted with inflammatory or infectious diseases. In a further aspect, the present. . .

SUMM An exemplary nitric oxide scavenger contemplated for use in the practice of the present invention is a **dithiocarbamate**-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble **dithiocarbamate**-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by. . . methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. **Dithiocarbamate**-containing nitric oxide scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable **dithiocarbamate**-metal-NO complex. Whereas free .NO is a potent vasodilator, the .NO chelated with **dithiocarbamate**-iron complexes is not. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by. . .

DRWD . . . collectively illustrates the effects of .NO inhibitors on ex-vivo 9.5-GHz EPR spectra of the [(MGD).sub.2 /Fe-NO] complex (MGD is N-methyl-D-glucamine **dithiocarbamate**) detected in the urine of normal mice. The mice were injected subcutaneously with 0.4 mL of the [(MGD).sub.2 /Fe] complex. . .

DETD administering to a subject an effective amount of at least one **dithiocarbamate**-containing nitric oxide scavenger.

DETD **Dithiocarbamate**-containing nitric oxide scavengers

contemplated for use in the practice of the present invention include any physiologically compatible derivative of the **dithiocarbamate** moiety (i.e., (R).sub.2 N--C(S)--SH). Such compounds can be described with reference to the following generic structure:

DETD . . . the like (e.g., Fe.sup.+2, Fe.sup.+3, Co.sup.+2, Co.sup.+3, Cu.sup.+2, Mn+.sup.2 or Mn.sup.+3). In accordance with the present invention, the ratio of **dithiocarbamate**-species to counter-ion M can vary widely. Thus, **dithiocarbamate**-containing nitric oxide scavenger can be administered without any added metallic counter-ion (i.e., M=H.sup.+, or a transition metal cation to **dithiocarbamate**-species ratio of zero), with ratios of transition metal cation to **dithiocarbamate**-species up to about 1:2 (i.e., a 2:1 **dithiocarbamate**:transition metal cation complex) being suitable.

DETD administering to a subject an effective amount of at least one **dithiocarbamate**-containing nitric oxide scavenger.

DETD In accordance with a particular aspect of the present invention, the **dithiocarbamate**-containing nitric oxide scavenger is administered in combination with a cytokine (e.g., IL-1, IL-2, IL-6, IL-12, TNF or interferon-.gamma.), an antibiotic. . . detrimental side effects of many of the above-noted pharmaceutical agents (e.g., systemic hypotension) can be prevented or reduced by the **dithiocarbamate**-containing nitric oxide scavenger. Thus, a patient being treated with any of the above-described agents could be monitored for evidence of. . . overproduction (e.g., blood pressure drop). At the first evidence of such overproduction, co-administration of a suitable dose of the above-described **dithiocarbamate** -containing nitric oxide scavenger could be initiated, thereby alleviating (or dramatically reducing) the side-effects of the primary therapy.

DETD Those of skill in the art recognize that the **dithiocarbamate** -containing nitric oxide scavengers described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously,. . .

DETD . . . administration and dosage employed for each subject is left to the discretion of the practitioner. In general, the dosage of **dithiocarbamate**-containing nitric oxide scavenger employed in the practice of the present invention falls in the range of about 0.01 mmoles/kg body. . .

DETD . . . delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like. As noted above, compounds of structure I (i.e., **dithiocarbamate**-species free of transition metal cations) can be employed directly in the practice of the present invention, or pre-formed **dithiocarbamate**-transition metal chelates (i.e., compounds of structure II) having varying ratios of transition metal to **dithiocarbamate**-species can be employed in the invention methods.

DETD Depending on the mode of delivery employed, the **dithiocarbamate** -containing nitric oxide scavenger can be delivered in a variety of pharmaceutically acceptable forms. For example, the scavenger can be delivered. . .

DETD Also contemplated are compositions representing a combination of compounds of structure I and compounds of structure II, i.e., **dithiocarbamate** species wherein the ratio of M.sup.+1 : **dithiocarbamate**-species is less than 1:1 and the ratio of M.sup.+2,+3 :**dithiocarbamate**-species is less than 1:2. A presently preferred composition is one wherein the ratio of M.sup.+2,+.sup.3 :**dithiocarbamate**-species is about 1:5 (i.e., about 40% of the **dithiocarbamate**-species are incorporated into a **dithiocarbamate**:transition metal cation complex, while about

60% of the **dithiocarbamate**-species exist in monovalent form).

DETD N-Methyl-D-glucamine and carbon disulfide were obtained from Aldrich (Milwaukee, Wis.). N-Methyl-D-glucamine **dithiocarbamate** (MGD) was synthesized by following the method of Shinobu et al. (Acta Pharmacol. Toxicol. 54:189-194 (1984)).

DETD . . . in the red blood cells, thereby reducing nitrate levels in the plasma. These results demonstrate that the administration of a **dithiocarbamate**-containing nitric oxide scavenger, such as the [(MGD).sub.2 /Fe] complex, is effective to reduce in vivo .NO levels in LPS-treated mice.

DETD . . . the [(MGD).sub.2 /Fe-NO] complex was also detected in the urine. This suggests that regardless of the route of administration employed, **dithiocarbamate**-containing nitric oxide scavengers, such as the [(MGD).sub.2 /Fe] complex, are capable of interacting with the .NO produced in vivo to form a **dithiocarbamate**-Fe-NO complex, which reduces in vivo .NO levels.

DETD . . . released by excess .NO production, which is known to attack cellular iron-containing proteins and result in cellular iron loss during **sepsis** or septic shock. This example shows that MGD, either with or without added iron, is effective for the treatment of. . .

CLM What is claimed is:

. . . nitric oxide levels in a subject, said method comprising: administering to said subject an effective amount of at least one **dithiocarbamate**-containing nitric oxide scavenger, wherein said **dithiocarbamate**-containing nitric oxide scavenger comprises a **dithiocarbamate** moiety and, optionally a physiologically compatible di- or tri-valent transition metal ion, wherein said **dithiocarbamate** has the structure: R.sub.1 R.sub.2 N--C(S)--S wherein: each of R.sub.1 and R.sub.2 is independently selected from a C.sub.1 up to. . .

. . . nitric oxide overproduction in a subject, said method comprising: administering to said subject an effective amount of at least one **dithiocarbamate**-containing nitric oxide scavenger, wherein said **dithiocarbamate**-containing nitric oxide scavenger comprises a **dithiocarbamate** moiety and, optionally, a physiologically compatible di- or tri-valent transition metal ion, wherein said **dithiocarbamate** has the structure: R.sub.1 R.sub.2 N--C(S)--S wherein: each of R.sub.1 and R.sub.2 is independently selected from a C.sub.1 up to. . .

8. A method according to claim 2 wherein the ratio of transition metal ion to **dithiocarbamate** moiety falls in the range of zero up to about 1:2.

10. A method according to claim 2 wherein said **dithiocarbamate** -containing nitric oxide scavenger is administered in combination with a cytokine, an antibiotic, a vasoactive agent, or mixtures thereof.

13. A method according to claim 2 wherein said **dithiocarbamate** -containing nitric oxide scavenger is delivered orally, intravenously, subcutaneously, parenterally, rectally or by inhalation.

14. A method according to claim 2 wherein said **dithiocarbamate** -containing nitric oxide-scavenger is delivered in the form of a solid, solution, emulsion, dispersion, micelle or liposome.

23. A composition according to claim 22 wherein the ratio of transition metal ion to **dithiocarbamate** moiety falls in the range of zero up to about 1:2.

L4 ANSWER 19 OF 23 USPATFULL
AN 1998:4601 USPATFULL
TI Macrocyclic immunomodulators
IN Luly, Jay R., Libertyville, IL, United States
Kawai, Megumi, Libertyville, IL, United States
Or, Yat Sun, Libertyville, IL, United States
Wiedeman, Paul, Libertyville, IL, United States
Wagner, Rolf, Gurnee, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5708002 19980113
AI US 1996-734793 19961023 (8)
RLI Continuation of Ser. No. US 1995-531534, filed on 21 Sep 1995 which is a division of Ser. No. US 1993-149416, filed on 9 Nov 1993, now patented, Pat. No. US 5457111 which is a continuation-in-part of Ser. No. US 1993-32958, filed on 17 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1991-755208, filed on 5 Sep 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Bond, Robert T.
LREP Steele, Gregory W.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1,4
DRWN No Drawings
LN.CNT 7023
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Immunomodulatory macrocyclic compounds having the formula ##STR1## and pharmaceutically acceptable salts, esters, amides and prodrugs thereof, wherein X is selected from one of the formulae ##STR2## as well as pharmaceutical compositions containing the same.
SUMM . . . alkali burn; dermatitis such as erythema multiforme, linear IgA ballous dermatitis and cement dermatitis; and others such as gingivitis, periodontitis, **sepsis**, pancreatitis, diseases caused by environmental pollution (for example, air pollution), aging, carcinogenis, metastasis of carcinoma and hypobaropathy; disease caused by. . .
SUMM . . . substituted carbonyl or an alpha substituted masked carbonyl group of a corresponding compound with an appropriate thioamide, thiourea or with **dithiocarbamic** acid derivatives, where the alpha substituent L is a leaving group.

L4 ANSWER 20 OF 23 USPATFULL
AN 97:112451 USPATFULL
TI Malonic acid derivatives having antiadhesive properties
IN Toepfer, Alexander, Hofheim, Germany, Federal Republic of
Kretzschmar, Gerhard, Eschborn, Germany, Federal Republic of
Bartnik, Eckart, Wiesbaden, Germany, Federal Republic of
Seiffge, Dirk, Mainz-Kostheim, Germany, Federal Republic of
PA Hoechst Aktiengesellschaft, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
PI US 5693621 19971202
AI US 1995-403525 19950313 (8)
PRAI DE 1994-4408248 19940311
DE 1994-4430005 19940825
DT Utility
FS Granted
EXNAM Primary Examiner: Peselev, Elli
LREP Foley & Lardner
CLMN Number of Claims: 20

ECL Exemplary Claim: 1,18,19
DRWN No Drawings
LN.CNT 1154
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to malonic acid derivatives, which inhibit the binding of selectin to carbohydrate ligands, and pharmaceutical compositions and diagnostic agents containing these derivatives, and methods for using these pharmaceutical compositions and diagnostic agents.
SUMM . . . (1990)). Carbohydrate mimetics are thus expected to have efficacy in the prevention and treatment of bacterial and viral infections and **sepsis**.
DETD . . . e.g., monallylated diol, can be synthesized from these compounds. Alternatively, a linkage (amide, ester, amine, thioether, thioester, urethane, xanthate or **dithiocarbamate**) other than the ether bond can be selected. The second functional group is then glycosylated using an activated monosaccharide component,. . .

L4 ANSWER 21 OF 23 USPATFULL
AN 97:106809 USPATFULL
TI Non-glycopeptide antimicrobial agents in combination with an anticoagulant, an antithrombotic or a chelating agent, and their uses in, for example, the preparation of medical devices
IN Raad, Isaam, Houston, TX, United States
Sherertz, Robert, Winston-Salem, NC, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
Baylor College of Medicine, Houston, TX, United States (U.S. corporation)
Wake Forest University, Winston-Salem, NC, United States (U.S. corporation)
PI US 5688516 19971118
AI US 1994-317309 19941003 (8)
RLI Continuation-in-part of Ser. No. US 1993-150472, filed on 12 Nov 1993, now abandoned which is a continuation-in-part of Ser. No. US 1992-975486, filed on 12 Nov 1992, now patented, Pat. No. US 5362754
DT Utility
FS Granted
EXNAM Primary Examiner: Azpuru, Carlos
LREP Arnold, White & Durkee
CLMN Number of Claims: 51
ECL Exemplary Claim: 1
DRWN 12 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 2546
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods of employing compositions in flushing and coating medical devices are disclosed. The compositions include selected combinations of a chelating agent, anticoagulant, or antithrombotic agent, with an non-glycopeptide antimicrobial agent, such as the tetracycline antibiotics. Methods of using these compositions for coating a medical device and for inhibiting catheter infection are also disclosed. Particular combinations of the claimed combinations include minocycline or other non-glycopeptide antimicrobial agent together with EDTA, EGTA, DTPA, TTH, heparin and/or hirudin in a pharmaceutically acceptable diluent.
SUMM . . . essential in the management of hospitalized or chronically ill patients. Unfortunately, vascular catheters have become the major source for hospital-acquired **sepsis**. Hence, the benefit derived from indwelling medical devices such as vascular catheters is often upset by infectious complications. Thrombotic occlusions. . .

DETD Catheter surfaces were exposed to various catheter-related bloodstream isolates that commonly cause catheter **sepsis** such as Staphylococcus epidermidis, Staphylococcus aureus, Candida albicans, and Xanthomonas maltophilia. Equal size (0.3 cm.sup.2) silicone segments that were colonized. . .

DETD . . . catheters have been shown by a clinical study done by Maki et al. (1977) to reduce the rate of catheter-related **sepsis** five fold.

DETD . . . positive quantitative blood culture through the CVC in the absence of a positive peripheral blood culture or clinical manifestations of **sepsis** (fever, chills or hypotension). Patients in the study who develop fever will be evaluated, and simultaneous quantitative blood cultures through. . .

DETD Statistical Considerations: Based on a surveillance study conducted by the inventors (see Table 21), the rate of CVC-related **sepsis** in pediatric oncology patients ranges from 15%-20.5% (see Table 20). Assuming a conservative total infection rate of 15% and assuming. . .

DETD . . . (6)

intraluminal colonization			
Tunnel tract infection			
	2.6 (1)	N/A	0.7 (1)
Total	28.2 (11)	6.0 (6)	12.2 (17)
CATHETER-RELATED			
	7.7 (3)	2.0 (2)	3.6 (5)
SEPSIS			
Definite			
Probable & physician			
	12.8 (5)	13.0	12.9 (18)
diagnosed		(13)	
Total	20.5 (8)	15.0	16.5 (23)
		(15)	
#Catheters	N = 39	N = 100. . .	

DETD AMMONIUM-1-PYRROLIDINE **DITHIOCARBANATE**

L4 ANSWER 22 OF 23 USPATFULL
AN 95:90535 USPATFULL
TI Macrocyclic immunomodulators
IN Luly, Jay R., Libertyville, IL, United States
Kawai, Megumi, Libertyville, IL, United States
Or, Yat S., Libertyville, IL, United States
Wiedeman, Paul, Libertyville, IL, United States
Wagner, Rolf, Gurnee, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)
PI US 5457111 19951010
AI US 1993-149416 19931109 (8)
RLI Continuation-in-part of Ser. No. US 1993-32958, filed on 17 Mar 1993, now abandoned which is a continuation-in-part of Ser. No. US 1991-755208, filed on 5 Sep 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Bond, Robert T.
LREP Danckers, Andreas M., Crowley, Steven R.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 7685
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Immunomodulatory macrocyclic compounds having the formula ##STR1## and pharmaceutically acceptable salts, esters, amides and prodrugs thereof, wherein X is selected from one of the formulae ##STR2## as well as

pharmaceutical compositions containing the same.

SUMM . . . alkali burn; dermatitis such as erythema multiforme, linear IgA ballous dermatitis and cement dermatitis; and others such as gingivitis, periodontitis, **sepsis**, pancreatitis, diseases caused by environmental pollution (for example, air pollution), aging, carcinogenis, metastasis of carcinoma and hypobaropathy; disease caused by. . .

SUMM . . . substituted carbonyl or an alpha substituted masked carbonyl group of a corresponding compound with an appropriate thioamide, thiourea or with **dithiocarbamic** acid derivatives, where the alpha substituent L is a leaving group.

L4 ANSWER 23 OF 23 USPATFULL

AN 94:93083 USPATFULL

TI Method for the detection of nitric oxide

IN Lai, Ching-San, Brookfield, WI, United States

PA MCW Research Foundation, Inc., Milwaukee, WI, United States (U.S. corporation)

PI US 5358703 19941025

AI US 1993-127665 19930927 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Bhat, Nina

LREP Quarles & Brady

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN 8 Drawing Figure(s); 8 Drawing Page(s)

LN.CNT 579

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of detecting nitric oxide in an aqueous body fluid of a mammal comprises introducing into the body fluid the agents required to form a water-soluble, stable, paramagnetic complex with nitric oxide and then subjecting the body fluid to magnetic resonance methods which can detect the complex to determine if any nitric oxide was present. A paramagnetic complex containing nitric oxide also is described, as well as, a method of diagnosing septic shock in a mammal by stabilizing and detecting the presence of nitric oxide in a body fluid of the mammal.

SUMM . . . surgical procedures, extensive use of immunosuppressive and chemotherapeutic agents, and increasing prevalence of chronic debilitating conditions. Because the mechanisms underlying **sepsis** and septic shock are not yet known, therapeutic interventions have been largely ineffective.

SUMM . . . of the present invention is the complex which is formed with nitric oxide when a metal-chelator, preferably consisting of N-methyl-D-glucamine **dithiocarbamate** (MGD) and reduced iron (Fe.sup.2+), is formed in or added to a body fluid containing nitric oxide (.NO).

DETD . . . a body fluid, is trapped and stabilized for up to 30 minutes by injecting a metal-chelator, preferably consisting of N-methyl-D-glucamine **dithiocarbamate** (MGD) and reduced iron (Fe.sup.2+), intravenously into a body fluid of a mammal to form a stable and water-soluble paramagnetic. . .

DETD . . . assay (2). NO.sub.3.sup.- was first converted to NO.sub.2.sup.- by E. coli nitrate reductase (3) and measured as described above. N-methyl-D-glucamine **dithiocarbamate** (MGD) was synthesized by following the method of Shinobu et al. (4).

DETD As demonstrated in Example 2 the spin-trapping technique employing a water-soluble metal-chelator, such as a **dithiocarbamate** derivative chelated with reduced iron, combined with 3.5 GHz (S-band) EPR spectroscopy is suitable for studying in vivo .NO production. . .

DETD Iminodiacetic acid **dithiocarbamate** and its trisodium salt;
DETD sarcosine **dithiocarbamate** and disodium salt;
DETD di(hydroxyethyl)**dithiocarbamate** and its monosodium salt.
DETD N-benzyl-D-glucamine **dithiocarbamate**;
DETD N-iso-amyl-N-glucamine **dithiocarbamate**;
DETD N-(4-methylbenzyl)-D-glucamine **dithiocarbamate**;
DETD Proline **dithiocarbamate**; and
DETD N-p-isopropylbenzyl-D-glucamine **dithiocarbamate**.
CLM What is claimed is:
. . . adding to said body fluid an effective amount of a chelating agent selected from the group consisting of iminodiacetic acid **dithiocarbamate** and its trisodium salt; sarcosine **dithiocarbamate** and its disodium salt; di(hydroxyethyl) **dithiocarbamate** and its monosodium salt; N-methyl-D-glucamine **dithiocarbamate**; N-benzyl-D-glucamine **dithiocarbamate**; N-iso-amyl-N-glucamine **dithiocarbamate**; N-(4-methylbenzyl)-D-glucamine **dithiocarbamate**; proline **dithiocarbamate**; and N-p-isopropylbenzyl-D-glucamine **dithiocarbamate**; which will combine with any such amounts of nitric oxide and any metallic ions which act like reduced iron ions. . .
. . . suspected of having septic shock, an effective amount of a chelating agent selected from the group consisting of iminodiacetic acid **dithiocarbamate** and its trisodium salt; sarcosine **dithiocarbamate** and its disodium salt; di(hydroxyethyl) **dithiocarbamate** and its monosodium salt; N-methyl-D-glucamine **dithiocarbamate**; N-benzyl-D-glucamine **dithiocarbamate**; N-iso-amyl-N-glucamine **dithiocarbamate**; N-(4-methylbenzyl)-D-glucamine **dithiocarbamate**; proline **dithiocarbamate**; and N-p-isopropylbenzyl-D-glucamine **dithiocarbamate**; and an effective amount of a nontoxic, iron ion to combine with any overproduced nitric oxide present in the body. . .
. . . introducing into said body fluid an effective amount of a chelating agent selected from the group consisting of iminodiacetic acid **dithiocarbamate** and its trisodium salt; sarcosine **dithiocarbamate** and its disodium salt; di(hydroxyethyl) **dithiocarbamate** and its monosodium salt; N-methyl-D-glucamine **dithiocarbamate**; N-benzyl-D-glucamine **dithiocarbamate**; N-iso-amyl-N-glucamine **dithiocarbamate**; N-(4-methylbenzyl)-D-glucamine **dithiocarbamate**; proline **dithiocarbamate**; and N-p-isopropylbenzyl-D-glucamine **dithiocarbamate**; which combines with nitric oxide and reduced iron ions to form a water-soluble paramagnetic complex which can be detected by. . .

L6 ANSWER 32 OF 34 USPATFULL
PI US 4879109 19891107 <--
SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .
SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW755C, nafazatrom, prostacyclin, iloprost, allopurinol, phenytoin as well as other antiinflammatory or cytoprotective drugs. It is to be understood that. . .
DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .

L6 ANSWER 33 OF 34 USPATFULL
PI US 4439445 19840327 <--
SUMM . . . prior episode of gastric or duodenal ulcer disease. Other such subjects include patients under severe physical conditions such as shock, **sepsis**, burns, multiple fractures, accident injuries with trauma (head, chest, abdomen, etc.), hemorrhage, extensive and prolonged surgical interventions, and organ transplants.
SUMM . . . humans being treated with NOSAC such as aspirin, indomethacin, phenylbutazone, mefenamic acid, flufenamic acid, naproxen, 2-phenoxyphenylpropionic acid, (+)-3-chloro-4-cyclohexyl-.alpha.-methylphenylacetic acid, and **ibuprofen**.

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(FILE 'HOME' ENTERED AT 12:55:12 ON 22 JUL 2002)

FILE 'USPATFULL' ENTERED AT 12:55:20 ON 22 JUL 2002
L1 3847 S SEPSIS
L2 1600 S DITHIOCARBO?
L3 1 S L1 AND L2
L4 23 S L1 AND DITHIOCARBA?
L5 191 S IBUPROFEN AND L1
L6 34 S L5 AND PD<1995

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L6 ANSWER 1 OF 34 USPATFULL
PI US 5756449 19980526
WO 9320102 19931014 <--
SUMM **Sepsis**/septic shock;
DETD . . . an anti-inflammatory agent. Peptide T would therefore be a novel non-steroidal anti-inflammatory drug (NSAID). Tradiational NSAIDs, such as aspirin and **ibuprofen**, have two potential mechanisms of action: inhibition of cyclooxygenase reducing prostaglandin production and inhibition of neutrophil function (Altman R. D.. . .

L6 ANSWER 2 OF 34 USPATFULL
PI US 5532230 19960702
WO 9420111 19940915 <--

SUMM . . . dermal perfusion and allow other prostaglandin synthesis, which would circumvent detrimental effects of the anti-inflammatory agents (11). Therapeutic doses of **ibuprofen** and imidazole were found to prevent dermal vascular occlusion by acting as an antagonist to a plasmin inhibitor (14). The. . .

SUMM . . . cellular damage and necrotic tissue correlates with development of bacterial translocation (23). The clinically important repercussions of bacterial translocation are **sepsis** and multi-system organ failure (22-24). The incidence of **sepsis** and disseminated organ involvement following stress is greatest among patients that also exhibit compromised immune defenses (22, 23), such as. . .

L6 ANSWER 3 OF 34 USPATFULL
PI US 35053 19951010
US 5099019 19920324 (Original) <--

DETD . . . as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . upper gastrointestinal bleeding; such bleeding is likely to be prevented or stopped by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 4 OF 34 USPATFULL
PI US 5366505 — 19941122 <--

SUMM . . . previously considered a non-pathogenic organism. It has now emerged as the most common cause of foreign body infection and nosocomiai **sepsis**. It is the major cause of prosthetic valve endocarditis, vascular graft infection, artificial hip and knee infection, and catheter related **sepsis**. Although less virulent than S. aureus and many other bacteria, it is highly resistant to most antimicrobials except vancomycin and. . .

DETD . . . by such microorganisms reduces their ability to adhere to the medical device thus reducing the risk of infection and nosocomial **sepsis**.

DETD . . . that by inhibiting the adherence of bacteria to catheters and other medically related foreign bodies, the risk of infection and **sepsis** can be reduced, and the residence time in which the medical device can remain in the body can be increased.. . .

DETD . . . such as acetylsalicylic acid (aspirin), salicylate, bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, **ibuprofen**, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone,. . .

DETD . . . pH Count/Plate CFU/mm

Coagulase Negative Staphylococci (Polyurethane - tubing)			
Control	7.33	>400	20.0
Salicylate 200 mM	7.19	310	14.6
Salicylate 600 mM	6.77	50	2.4
Ibuprofen 400 mM	7.22	233	11.5
Ibuprofen 200 mM			

	7.02	352	18.1
E. coli (silastic tubing)			
Control		250	12.0
Salicylate 200 mM		226	11.6
Salicylate 600 mM		32	1.6
Ibuprofen 400 mM		238	12.0
Ibuprofen 200 mM		185	9.6

DETD Catheters treated with salicylate and **ibuprofen** as described in Example 9 were incubated in phosphate buffered saline having a concentration of 10.sup.3 CFU/ml E. coli for. . .

DETD

Coating	(CFU/plate)	Inhibition
Control	240	
200 mM salicylate	121	50%
100 mM **Ibuprofen**	70	71%

DETD Despite six days of incubation, the inhibition was impressive. It was greater with **ibuprofen** than salicylate in this experiment.

DETD Polyurethane and silastic catheters were incubated in **ibuprofen**, acetyl-salicylate, and benzoyl-benzoic acid with 95% ethanol for 2 hours. The catheters were then incubated in S. epidermidis as described. . .

DETD

	CFU/plate)	Inhibition
Polyurethane		
Control	295	
Acetyl-Salicylate (200 mM)	127	57%
Salicylate (200 mM)	270	9%
Ibuprofen (100 mM)	166	44%
Benzyl benzoic (100 mM)	333	0%
Silastic		
Control	52	
Acetyl-Salicylate (200 mM)	7	86%
Salicylate (200 mM)	33	36%
Benzyl benzoic (100. . .		

DETD

	Units of light (measured at 48.degree.)
Control	.62
Salicylate	.19
Acetylsalicylate	.06
Acetaminophen	2.4
Ibuprofen	.32
Phenylbutazone	.02
Indomethacin	.07

DETD

	Units of light (measured at 48.degree.)
Control	89.0
Acetylsalicylate	13.0
Salicylate	15.0
Ibuprofen	9.0
Acetaminophen	108.0
Indomethacin	9.2
Phenylbutazone	19.1

CLM What is claimed is:

. . . of salicylic acid, acetylsalicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, **ibuprofen**, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone,. . .

8. A device according to claim 6 wherein said NSAID is **ibuprofen** .

11. A device according to claim 9 wherein said NSAID is selected from the group consisting of salicylic acid, acetylsalicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, **ibuprofen**, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone,. . .

. . . of salicylic acid, acetylsalicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, difunisal, fendosal, indomethacin, acemethacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, **ibuprofen**, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone,. . .

18. A device according to claim 16 wherein said NSAID is **ibuprofen**.

19. A device according to claim 10 wherein said NSAID is selected from the group consisting of salicylic acid, acetylsalicylic acid (aspirin), bis-salicylate, benzyl-benzoic acid, diflunisal, fendosal, indomethacin, acemetacin, cinmetacin, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, isoxepac, **ibuprofen**, flurbiprofen, naproxen, ketoprofen, fenoprofen, benoxaprofen, indoprofen, pirprofen, carprofen, mefenamic acid, flufenamic acid, meclofenamate, niflumic acid, tolfenamic acid, flunixin, clonixin, phenylbutazone,. . .

L6 ANSWER 5 OF 34 USPATFULL

PI US 5348953 19940920 <--

SUMM . . . conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, chronic bronchitis, glomerulonephritis, osteoarthritis, spondylitis, lupus, psoriasis, atherosclerosis, **sepsis**, septicemia, shock, myocardial infarction, reperfusion injury, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

DETD . . . such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, chronic or acute bronchitis, cystic fibrosis, adult respiratory, distress syndrome, atherosclerosis, **sepsis**, septicemia, shock, periodontitis, glomerular nephritis or nephosis, myocardial infarction, reperfusion injury, infectious arthritis, rheumatic fever and the like, and may. . .

DETD . . . intended to include, but are not limited to aspirin, diflunisal, naphthylsalicylate, phenylbutazolone, oxyphenbutazolone, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, **ibuprofen**, naproxen, fenoprofen and piroxicam.

L6 ANSWER 6 OF 34 USPATFULL

PI US 5334380 19940802 <--

SUMM . . . Antagonist of Platelet Activating Factor in Endotoxin Shock, European J. Pharmacology, 135:117), and prostacyclin synthesis inhibitors (Wise, et al. (1985), **Ibuprofen**, Methylprednisolone, and Gentamycin as Cojoint Therapy in Septic Shock, Circ. Shock, 17:59) are protected against septic shock. However, the relative. . .

SUMM . . . can potentially prevent all of the biological responses to endotoxin or cytokines. This breadth of action is desirable in severe **sepsis**.

DETD . . . the present therapeutic regimens and methods for the treatment of hypotension, such as in a patient or animal with systemic **sepsis**, the following symptoms will be monitored: fever or hypothermia (temperature >38.3.degree. C. [101.degree. F.] or <35.6.degree. C. [96.degree. F.]; tachycardia. . .

DETD . . . patients with cancer (Khazaeli et al. J. Biol. Response Mod. 9:178-84, 1990) and in unblinded fashion to 34 patients with **sepsis**, (Fisher et al. Crit. Care Med. 18:1311-5, 1990) as well as to the 291 patients who received it in the. . .

DETD . . . Bahrami et al. In: Program and Abstracts of the Second International Congress on the Immune Consequences of Trauma, Shock, and **Sepsis**: Mechanisms and Therapeutic Approaches; Mar. 6-9, 1991; Munich, Germany, Abstract). Thus, TNF.alpha. is believed to play a central role in the development of **sepsis**, and administration of anti-TNF.alpha. antibodies appears to be an attractive method for improving outcome, particularly when used in conjunction with. . .

DETD . . . major potential benefit of monoclonal antibodies to TNF.alpha. is that such treatment may improve outcome in both gram-negative and gram-positive **sepsis**. Several factors may limit the success of this agent, however. First, TNF.alpha. levels have been detected in only about one. . . 1990; Sun et al. Am. J. Pathol. 136:949-956, 1990). Third, anti-TNF.alpha. antibodies may not be effective against all causes of **sepsis**.

DETD . . . antibodies may be prepared as described by Calandra et al. (1991), In: Bacterial Endotoxins: Cytokines Mediators and New Therapies for **Sepsis**, pp. 141-159), which reference is specifically incorporated herein by reference for this purpose. By way of example, such anti-tumor necrosis. . .

DETD 8. Roger C. Bone (1991), A Critical Evaluation of New Agents for the Treatment of **Sepsis**. JAMA, 266(12):1686-1691.

DETD . . . M. et al. (1991), Efficacy of Anti-lipopolysaccharide and Anti-Tumor Necrosis Factor Monoclonal Antibodies in a Neutropenic Rat Model of Pseudomonas **Sepsis**. J. Clin. Invest., 88:885-890.

DETD . . . Factor/Cachectin Antibodies for the Treatment of Gram-Negative Bacteremia and Septic Shock, In Bacterial Endotoxins: Cytokine Mediators and New Therapies for **Sepsis**, pp. 141-159.

L6 ANSWER 7 OF 34 USPATFULL

PI US 5322943 19940621 <--
DETD . . . as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . upper gastrointestinal bleeding; such bleeding is likely to be prevented or stopped by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 8 OF 34 USPATFULL
PI US 5321041 19940614 <--
SUMM Since early 1970's, various non-steroidal anti-inflammatory agents, representative examples of such agents include indomethacin and **ibuprofen**, have been developed. The mechanisms of action of these drugs are mainly based on their inhibitory activities on the generation. . .
SUMM . . . peptic ulcer, alcoholic hepatitis, cirrhosis, fatty liver, cancer, side effects of anti-cancer agent, retinopathy, cataract, obesity, gestosis, radiation injury, shock, **sepsis** and various senile regressive diseases.
SUMM TABLE 5

Test Drug (Compound No.)	Dose (mg/kg)	Inhibition on Edema (%)
114	30	41.9
175	30	50.6
176	30	30.6
188	30	55.0
195	30	43.9
Ibuprofen	100	0

L6 ANSWER 9 OF 34 USPATFULL
PI US 5310551 19940510 <--
SUMM . . . progression of hyperoxic lung damage in mice. Das et al, Biomed. Biochim. Acta 47(12):1023-1036 (1988), describe a study demonstrating that **ibuprofen** cannot prevent hyperoxic lung injury although it inhibits the influx of PMN into the injured lung, suggesting that PMN are. . .
SUMM . . . rabbits. Vedder et al, J. Clin, Invest. 81: 939 (1988). Anti-CD18 antibodies have been shown not to increase susceptibility to **sepsis** when used to inhibit neutrophil adherence in rabbits. Mileski et al, Surgical Forum, Infection and its Mediators, p. 107 (1989).

L6 ANSWER 10 OF 34 USPATFULL
PI US 5296353 19940322 <--
SUMM . . . by the development of an impaired immune response. Progressive immunosuppression has been observed in patients with acquired immunodeficiency syndrome (AIDS), **sepsis**, leprosy, cytomegalovirus infections, malaria, etc. The mechanisms responsible for the down-regulation of the immune response, however, remain to be elucidated.
DETD . . . variety of infections including those that are intracellular such as leprosy, tuberculosis, leishmania, etc.; those that are extracellular such as **sepsis**, etc; diseases of viral etiology such as those caused by HIV, cytomegalovirus, Epstein Barr, etc.;

parasitic infections such as schistosomiasis,. . .
DETD . . . which reduce tumor size or load including cyclophosphamide, adriamycin, steroids, etc.; growth hormones; cimetidine; chloroquine; non-steroidal anti-inflammatories such as aspirin, **ibuprofen**, indomethacin, etc.; levamisole; etc.

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L6 ANSWER 11 OF 34 USPATFULL
PI US 5284645 19940208 <--
SUMM . . . by thromboxane synthetase. Imidazole inhibits thromboxane synthetase and prevents the synthesis of TxA.sub.2 ; other agents, such as aspirin-like compounds, **ibuprofen** and indomethacin, inhibit cyclo-oxygenase, thus preventing the synthesis of all the prostanoids.
SUMM . . . inflammatory response comprising vasodilation, edema and pain. A comparative study of the effectiveness of inflammation suppression by imidazole, indomethacin, and **ibuprofen** by Schirmer, W et al. Current Surgery March-April, 1987, pp. 102-105) in a model system of acute peritoneal **sepsis** indicated that imidazole, which inhibits only the formation of thromboxane A2, maintained its activity in preventing endotoxic shock over a. . .
SUMM . . . fluorocarbon emulsions is frequently accompanied by a transient fever and inflammatory response. I have found that agents such as imidazole, **ibuprofen** and indomethacin have an anti-pyretic effect which mitigates the inflammatory response when they are present in these emulsions.
DETD . . . (dazoxiben) or imidazo(1,5-.alpha.)pyridine-5-hexanoic acid (CGS 13080). The fluorocarbon emulsion may further comprise an anti-inflammatory agent which is aspirin, indomethacin, or **ibuprofen**. The emulsion can be one which is capable of carrying oxygen to the tissues.
DETD According to another aspect of the invention, there is provided a method of treatment of the medical conditions of **sepsis**, endotoxin shock, hemorrhagic shock or blood loss, pulmonary hypertension or other complications of **sepsis**, or thrombosis, for example, following thrombolysis for acute myocardial infarction, comprising the introduction of such emulsions into the bloodstream of. . .
DETD . . . in similarly treated normal rabbits. It has been found that the symptoms can be alleviated by cyclo-oxygenase inhibitors such as **ibuprofen**. The data of Examples 1, 2 and 3 indicate that the thromboxane synthetase-inhibiting action of imidazole incorporated into 100% (w/v). . .
DETD Other anti-inflammatory agents, comprising aspirin (acetylsalicylic acid) or other salicylates, indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) and **ibuprofen** ((.+-.)-2-(p-isobutylphenyl)propionic acid) may usefully be added to imidazole or histidine-containing fluorocarbon emulsions in established therapeutic concentrations to enhance the anti-inflammatory. . . in amounts sufficient to establish a total dose of 300 to 1000 mg of aspirin; 200 to 1200 mg of **ibuprofen**; and 10 to 100 mg of indomethacin.

L6 ANSWER 12 OF 34 USPATFULL
PI US 5268477 19931207 <--
DETD . . . as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . upper gastrointestinal bleeding;

such bleeding is likely to be prevented or stopped by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 13 OF 34 USPATFULL
PI US 5264220 19931123 <--
DETD . . . can also be any cyclooxogenase inhibitor, known or to be discovered in the future, with the preferred cyclooxogenase inhibitor being **ibuprofen**.
DETD . . . treat conditions such as anemia, hypoxia or hypoxemia. These conditions are often brought about by disorders such as hemorrhagic shock, **sepsis**, trauma and myocardial infarction.
DETD When **ibuprofen** is administered orally, the dosage should be about 10 mg/kg/day to about 40 mg/kg/day. When **ibuprofen** is administered by the preferred parenteral mode, an initial bolus injection of about 10 mg/kg should be followed by an. . .
DETD . . . with three other vascular dwell-time enhancing agents: isoniazid, nicotinic acid and neomycin. A fourth experiment focused on the effects of **ibuprofen** on the concentration of PFOB in the blood of healty mice as well as mice with mammary tumors or Lewis. . .
DETD . . . acid (Sigma) neomycin (Sigma) solutions were freshly prepared before each experiment. These compounds were dissolved in water and administered intravenously. **Ibuprofen** (Upjohn Co.) was obtained as sterile stable solution suitable for intravenous administration.
DETD In a fourth experiment, mice were administered three bolus doses of **ibuprofen** (10 mg/kg) intraperitoneally and a single intravenous bolus dose of PFOB (10 g/kg). Forty-eight hours post injection of PFOB, the. . .
DETD TABLE XV

The Effect of Three Doses of **Ibuprofen** on the Concentration of PFOB (mg/g) in Blood 48 Hours after the Administration of PFOB..sup.1

	Mean	S.E..sup.b	N.sup.c	p Value.sup.d	% Change
NORMAL MICE					
Saline Control	9.38	0.71	19		
Ibuprofen	18.56	3.61	18	<.01	49
MICE WITH MAMMARY TUMORS					
Saline Control	0.34	0.71	19		
Ibuprofen	1.94	3.61	18	<.05	83
MICE WITH LEWIS LUNG TUMORS					
Saline Control	1.67	0.71	19		
Ibuprofen	4.49	3.61	18	<.05	63

.sup.1 **Ibuprofen** was administered intraperitoneally 24 hours before, 30 minutes before and 24 hours after the intravenous administration of PFOB.
.sup.a S.D.. . . a onesided Student ttest comparing a saline control therapy with the results of the other categories of therapy (such as **ibuprofen**).
DETD The results of Experiment 4 demonstrate that **ibuprofen** is also

capable of increasing the concentration of PFOB within the blood. As noted previously, the depressed levels of PFOB. . .

DETD It has been demonstrated that vascular dwell-time enhancing agents, such as nicotinamide, isoniazid, neomycin and **ibuprofen** are capable of extending the dwell-time of particulate therapeutic and diagnostic agents, such as PFOB, within the vascular compartment. These results suggest that nicotinamide, isoniazid, neomycin and **ibuprofen**, as well as other vascular dwell-time enhancing agents, are capable of enhancing the efficacy of a particulate therapeutic or a. . .

CLM What is claimed is:

. . . for preventing or treating hypoxia associated with (a) a mammalian disorder selected from the group consisting of hemorrhagic shock and **sepsis**, or (b) a medical procedure selected from the group consisting of angioplasty and cardiopulmonary bypass surgery, which method comprises the. . .

L6 ANSWER 14 OF 34 USPATFULL

PI US 5248697 19930928 <--

DETD . . . admission, the patient's serum level of acetaminophen was 224 mg/dL. The patient also consumed an unknown amount of barbiturates and **ibuprofen**. The standard therapy indicated for acetaminophen overdose, enteral administration of N-acetylcysteine, was not feasible for this patient due to gastrointestinal. . .

CLM What is claimed is:

. . . levels in said mammal is caused by a condition selected from the group consisting of cancer therapy, malnutrition, shock, infection, **sepsis** and anorexia.

L6 ANSWER 15 OF 34 USPATFULL

PI US 5229381 19930720 <--

SUMM . . . in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, glomercular nephrihs, myocardiol infection/reperfusion injury osteoarthritis, spondylitis, lupus, psoriasis, atherosclerosis, **sepsis**, septicemia, shock, periodontitis, cystic fibrosis, myocardial infarction, reperfusion injury, meningitis, glomerulonephritis and acute respiratory distress syndrome.

DETD . . . such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, chronic or acute bronchitis, cystic fibrosis, adult respiratory distress syndrome, atherosclerosis, **sepsis**, septicemia, shock, periodontitis, glomerular nephritis or nephosis, myocardial infarction, reperfusion injury, infectious arthritis, rheumatic fever and the like, and may. . .

DETD . . . intended to include, but are not limited to aspirin, diflunisal, naphthylsalicylate, phenylbutazolone, oxyphenbutazolone, indomethacin, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, **ibuprofen**, naproxen, fenoprofen and piroxicam.

L6 ANSWER 16 OF 34 USPATFULL

PI US 5208018 19930504 <--

SUMM It has been known for some time that in bacterial infection, **sepsis** and critical illness, bacterial lipopolysaccharides (LPS), or endotoxins, are responsible for many of the pathophysiological manifestations, including fever, malaise, anorexia,. . .

SUMM . . . produced acute illness with flu-like symptoms including fever, tachycardia, increased metabolic rate and stress hormone release. Since the cyclooxygenase inhibitor, **ibuprofen**, markedly attenuated these changes, the cyclooxygenase pathway was implicated as playing a role in critical illness. Michie, H. R. et. . .

SUMM . . . al., Ann. Surg. 208:493-503 (1988)). Unlike endotoxin responses, these effects peaked later, and resulted in increased circulating concentrations of interfon-.gamma.. **Ibuprofen** treatment attenuated the fever and stress hormone responses to IL2.

SUMM . . . in urine volume, fever, tachycardia and hypermetabolism, increased stress hormones, leukopenia, and hypoglycemia. Most of these changes were abolished by **ibuprofen** treatment. It was concluded that sublethal doses of TNF caused acute responses similar to endotoxemia/septicemia, and that cyclooxygenase inhibitors represent. . .

SUMM . . . (Br. J. Surg. 76:670- 671 (1989), reviewed evidence that TNF is the principal mediator associated with the changes of severe **sepsis**.

SUMM Gough et al. (Surgery 104:292-300 (1988)) studied burnt mice which are highly susceptible to bacterial **sepsis**. Mitogen-stimulated IL2 production by their spleen cells was impaired. Addition of exogenous rIL2 at 100 U/ml in vitro restored mitogen. . .

SUMM . . . the cachexia is associated with cancer. In other embodiments, the cachexia is associated with infectious diseases, including bacterial infection and **sepsis**, viral infection, such as with human immunodeficiency virus-1, and parasitic diseases. The invention is also directed to treating cachexia associated with catabolic states resulting from surgery, **sepsis**, burn injuries, calorie deprivation, chemotherapy, radiation therapy, uncontrolled diabetes, and complications of endotoxin stimulation such as renal failure, adult respiratory. . .

DETD . . . when administered intravenously to humans. TNF has also been proposed as a mediator of cachexia associated with AIDS, cancer and **sepsis**, and may directly induce tissue destruction.

DETD . . . (1977)), yet not all patients with high levels of endotoxin develop an acute-phase response. Similarly, the responses of individuals to **sepsis**, surgery and trauma, conditions often associated with acute-phase responses, vary considerably. It is important, therefore, to uncover a mechanism which. . .

DETD . . . Aderka et al., supra). Therefore, while it is recognized that TNF, or other cytokines, may be important in cancer and **sepsis** , measurement of plasma TNF levels has yielded little useful information for understanding why patients with similar tumor types and burdens. . .

DETD . . . why patients producing "normal" amounts of IL2 appear to fare better after endotoxin-associated critical illness, such as trauma, burns, and **sepsis** than patients showing an IL2 deficiency.

DETD . . . plays a role in modulating the human response to endotoxaemia which is frequently present in patients with cancer, surgery, trauma, **sepsis** or even occasionally in otherwise healthy subjects.

CLM What is claimed is:

9. The method of claim 1, wherein said cachexia occurs substantially associated with **sepsis**.

14. The method of claim 13, wherein said catabolic disorder is a result of surgery, **sepsis**, burn injuries, calorie deprivation, chemotherapy, radiation therapy, uncontrolled diabetes, or traumatic injury.

L6 ANSWER 17 OF 34 USPATFULL

PI US 5182106 19930126 <--

SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious

illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .

SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacyclin, iloprost, allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .

DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .

L6 ANSWER 18 OF 34 USPATFULL

PI US 5175281 19921229 <--

DETD . . . as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . upper gastrointestinal bleeding; such bleeding is likely to be prevented or stopped by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 19 OF 34 USPATFULL

PI US 5120843 19920609 <--

SUMM . . . as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . lead to upper gastrointestinal bleeding; such bleeding is likely to be prevented by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 20 OF 34 USPATFULL

PI US 5099019 19920324 <--

DETD . . . as nonsteroidal anti-inflammatory compounds (NOSAC). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . upper gastrointestinal bleeding; such bleeding is likely to be prevented or stopped by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 21 OF 34 USPATFULL

PI US 5071649 19911210 <--

SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .

SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacyclin, iloprost,

allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .

DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .

DETD . . . antiplatelet drugs, including but not limited to, heparin, aspirin, dipyridamole, ticlopidine and nonsteroidal antiinflammatory drugs including but not limited to **ibuprofen**, sulfinpyrazone with the surface active copolymer.

L6 ANSWER 22 OF 34 USPATFULL

PI US 5041288 19910820 <--

SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .

SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacyclin, iloprost, allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .

DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .

DETD . . . antiplatelet drugs, including but not limited to, heparin, aspirin, dipyridamole, ticlopidine and nonsteroidal antiinflammatory drugs including but not limited to **ibuprofen**, sulfinpyrazone with the surface active copolymer.

L6 ANSWER 23 OF 34 USPATFULL

PI US 5039520 19910813 <--

SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .

SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacyclin, iloprost, allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .

DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .

DETD . . . antiplatelet drugs, including but not limited to, heparin, aspirin, dipyridamole, ticlopidine and nonsteroidal antiinflammatory drugs including but not limited to **ibuprofen**, sulfinpyrazone with the surface active copolymer.

L6 ANSWER 24 OF 34 USPATFULL

PI US 5032394 19910716 <--
SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .
SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacyclin, iloprost, allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .
DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .
DETD . . . antiplatelet drugs, including but not limited to, heparin, aspirin, dipyridamole, ticlopidine and nonsteroidal antiinflammatory drugs including but not limited to **ibuprofen**, sulfinpyrazone with the surface active copolymer

L6 ANSWER 25 OF 34 USPATFULL
PI US 5030448 19910709 <--
SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .
SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacyclin, iloprost, allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .
DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial, parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .
DETD . . . antiplatelet drugs, including but not limited to, heparin, aspirin, dipyridamole, ticlopidine and nonsteroidal antiinflammatory drugs including but not limited to **ibuprofen**, sulfinpyrazone with the surface active copolymer.

L6 ANSWER 26 OF 34 USPATFULL
PI US 4997644 19910305 <--
SUMM . . . many other diseases. These conditions include acute or chronic infection, severe trauma, burns, sickle cell crisis, malaria, leukemia, myocardial infarction, **sepsis**, shock, and almost any serious illness which produces tissue damage or surgical maneuvers. Evidence indicates that the high concentrations of. . .
SUMM . . . copolymer can also be used with agents that prevent the generation of free radical species including, but not limited to, **ibuprofen**, BW 755C, nafazatrom, prostacylin, iloprost, allopurinol, phenytoin as well as other anti-inflammatory or cytoprotective drugs. It is to be understood. . .
DETD . . . red cell fragmentation syndrome, heat stroke, retained fetus, eclampsia, malignant hypertension, burns, crush injuries, fractures, trauma producing shock, major surgery, **sepsis**, bacterial,

parasitic, viral and rickettsial infections which promote activation of the coagulation system, central nervous system trauma, and during and. . .

DETD . . . antiplatelet drugs, including but not limited to, heparin, aspirin, dipyridamole, ticlopidine and nonsteroidal antiinflammatory drugs including but not limited to **ibuprofen**, sulfinpyrazone with the surface active copolymer.

L6 ANSWER 27 OF 34 USPATFULL
PI US 4996318 19910226 <--
WO 8807527 19881006 <--
SUMM . . . as nonsteroidal anti-inflammatory compounds (NOSAIDS). Stress ulcers are ulcers that develop after exposure to severe conditions such as trauma, burns, **sepsis**, extensive surgery, acute illnesses, and the like. Patients in intensive care units are particularly prone to develop stress ulcers. Stress. . . upper gastrointestinal bleeding; such bleeding is likely to be prevented or stopped by these compounds. NOSAC includes drugs such as **ibuprofen**, aspirin, indomethacin, naproxen, piroxicam and the like that are usually taken for analgesia, and that are often associated with gastrointestinal. . .

L6 ANSWER 28 OF 34 USPATFULL
PI US 4992365 19910212 <--
SUMM . . . Utsinger, N.J. Zvaifler, and G.E. Ehrlich eds., Rheumatoid Arthritis, J. B. Lippincott Co., 1985, especially Ch.1, pg. 4 under "Focal **Sepsis**", Ch.2, pp. 12-13, and Ch.3, pp. 21-22). In these references, the streptococcus, found consistently in the urine of arthritics using. . .
DETD . . . urinary sediment contained large numbers of encapsulated diplococci. On oral cephalexin (at a dosage of 1 gm per day) and **ibuprofen**, she realized major relief in a week. The cephalexin was continued. In two months the rheumatoid nodule began to shrink and it disappeared several months later. At three months, she only required 400 mg of **ibuprofen** a day to control her arthralgia. That month the diplococci reappeared and she had a mild flare-up. Both responded to. . .
DETD . . . and without warning. He had no other symptoms. The diagnosis elsewhere was RA. His urine contained cocci. On clindamycin and **ibuprofen** he had a remission in one week, but his urine continued to show "exploded" cocci. This finding cleared following a. . .

L6 ANSWER 29 OF 34 USPATFULL
PI US 4980160 19901225 <--
AB . . . invention relates to combinations of natural or recombinant tumor necrosis factors ("TNF") and non-steroidal anti-inflammatory agents, such as indomethacin and **ibuprofen**, useful for the growth inhibition or killing of transformed cells. According to this invention, the non-steroidal anti-inflammatory agents are used. . .
SUMM . . . invention relates to combinations of natural or recombinant tumor necrosis factors ("TNF") and non-steroidal anti-inflammatory agents, such as indomethacin and **ibuprofen**, useful for the growth inhibition or killing of transformed cells. According to this invention, the non-steroidal anti-inflammatory agents are used. . .
SUMM . . . clinically to treat human patients in endotoxic and hemorrhagic shock [B. L. Short et al., "Indomethacin Improves Survival In Gram-Negative **Sepsis**", Adv. Shock Res., 6, pp. 27-36 (1981); P. M. Almqvist et al., "Treatment Of Experimental Canine Endotoxin Shock With **Ibuprofen**, A Cyclooxygenase Inhibitor", Circ. Shock, 131, pp. 227-32 (1984); E. R. Jacobs, J. Clin. Invest., 70, pp. 536-41 (1982)

P.. . .

DRWD FIG. 3 is a graphical representation of the effect of treatment with TNF alone, **ibuprofen** alone, or a combination of TNF and **ibuprofen**, on the mortality (FIG. 3A) and body temperature (FIG. 3B) of CD strain male rats.

DETD . . . are not limited to, acetyl salicylic acid (aspirin), methyl salicylate, sodium salicylate, phenylbutazone, oxyphenbutazone, apazone, indomethacin, sulindac, tolmetin, mefenamic acid, **ibuprofen**, naproxen, fenoprofen, flurbiprofen, ketoprofen and other compounds having a similar ability to block prostaglandin, prostacyclin or thromboxane synthesis. Other anti-inflammatory. . .

DETD . . . dosage of about 25-50 mg, three times a day. Higher doses may also be used. Alternatively, aspirin (about 1500-2000 mg/day), **ibuprofen** (about 1200-3200 mg/day), or conventional therapeutic doses of other non-steroidal anti-inflammatory agents may be used. Dosages of non-steroidal anti-inflammatory agents. . .

DETD Group 4: 20 mg/kg body weight **ibuprofen** intraperitoneally; followed by 4 .mu.g/g body weight human recombinant TNF intravenously 2 hours later.

DETD Group 5: 20 mg/kg body weight **ibuprofen** intraperitoneally; phosphate buffered saline intravenously 2 hours later.

DETD . . . ng/mg endotoxin and had a specific activity in the range of about 9.6.times.10.sup.6 units/mg to 2.5.times.10.sup.7 units/mg. The indomethacin and **ibuprofen** were supplied by Sigma Co. and Upjohn Co., respectively.

DETD . . . before receiving TNF treatment, did not exhibit the symptoms seen in the Group 1 rats. Thus, indomethacin (Group 2) and **ibuprofen** (Group 4) were found to prevent the toxic effects of high dosage levels of TNF administration.

DETD The Group 4 rats, who received a single injection of **ibuprofen** before TNF treatment were also protected against the lethal effects of TNF. As demonstrated in FIG. 3A, 75% of the **ibuprofen**-treated rats were still alive 6 hours after the TNF injection. By 24 hours after TNF treatment, 55% of the rats. . .

DETD We believe that repeated administration of indomethacin or **ibuprofen** in the treatments described above would have further reduced any TNF induced mortality.

DETD Both indomethacin and **ibuprofen** prevented the rapid decrease in body temperature and the subsequent progressive hypothermia seen in animals treated with TNF alone. As demonstrated in FIGS. 1B and 3B, several of the rats treated with indomethacin or **ibuprofen** before TNF treatment showed only a slight decrease in body temperature--1.degree. or 2.degree. C.--which quickly returned to normal levels. Furthermore,. . .

DETD The Group 2 (indomethacin-treated) and Group 4 (**ibuprofen** -treated) rats exhibited neither peripheral cyanosis nor diarrhea.

DETD In addition, administration of indomethacin or **ibuprofen** before TNF treatment completely blocked the large rise in prostaglandin production, as reflected in the serum levels of the DHK-PG. . . treated with TNF alone. As demonstrated in Table 1, levels of this metabolite were extremely low in the indomethacin and **ibuprofen** -treated rats. By 3 hours after injection of the cyclooxygenase inhibitor, although DHK-PG levels were again detectable and approached normal values,. . .

DETD . . . seen in the TNF-treated rats of Group 1 were not seen in the rats receiving either an indomethacin or an **ibuprofen** injection prior to TNF treatment. As shown in FIG. 2, the Group 2 rats who received indomethacin did not show any significant changes in plasma glucose levels. **Ibuprofen** injection before TNF treatment also decreased the changes in blood glucose. Four hours after the TNF

treatment, those rats who had received **ibuprofen** had glucose levels which were about 40% lower than the untreated control rats. This decrease in blood glucose was much. . .

DETD The following Table 1 shows the effect of treatment with TNF alone, indomethacin alone, **ibuprofen** alone, or a combination of TNF and either indomethacin or **ibuprofen**, on plasma 13,14-dihydro-15-keto-PGE.sub.2 ("DHK-PG") levels of CD strain male rats.

DETD . . . 0.12 .+-. 0.02

TNF 2 hrs later
(Group 2)
Indomethacin and
0.35 .+-. 0.10
0.06 .+-. 0.01
0.12 .+-. 0.03

Saline 2 hrs later
(Group 3)
Ibuprofen and
0.17 .+-. 0.02
a.sup.2 0.69 .+-. 0.10

TNF 2 hrs later
(Group 4)
Ibuprofen and
0.17 .+-. 0.02
a.sup.2 0.64 .+-. 0.10

Saline 2 hrs later
(Group 5)

.sup.1 0 Time measurements were made immediately before. . .

CLM What is claimed is:

. . . from the group consisting of acetyl salicylic acid, methyl salicylate, sodium salicylate, phenylbutazone, oxyphenbutazone, apazone, indomethacin, sulindac, tolmetin, mefenamic acid, **ibuprofen**, naproxen, fenoprofen, flurbiprofen, ketoprofen, lipocortin and uromodulin.

. . . from the group consisting of acetyl salicylic acid, methyl salicylate, sodium salicylate, phenylbutazone, oxyphenbutazone, apazone, indomethacin, sulindac, tolmetin, mefenamic acid, **ibuprofen**, naproxen, fenoprofen, flurbiprofen, ketoprofen, lipocortin and uromodulin.

. . . from the group consisting of acetyl salicylic acid, methyl salicylate, sodium salicylate, phenylbutazone, oxyphenbutazone, apazone, indomethacin, sulindac, tolemetin, mefenamic acid, **ibuprofen**, naproxen, fenoprofen, flurbiprofen, ketoprofen, lipocortin and uromodulin.

18. The improvement of claim 15, wherein the anti-inflammatory agent is indomethacin or **ibuprofen**.